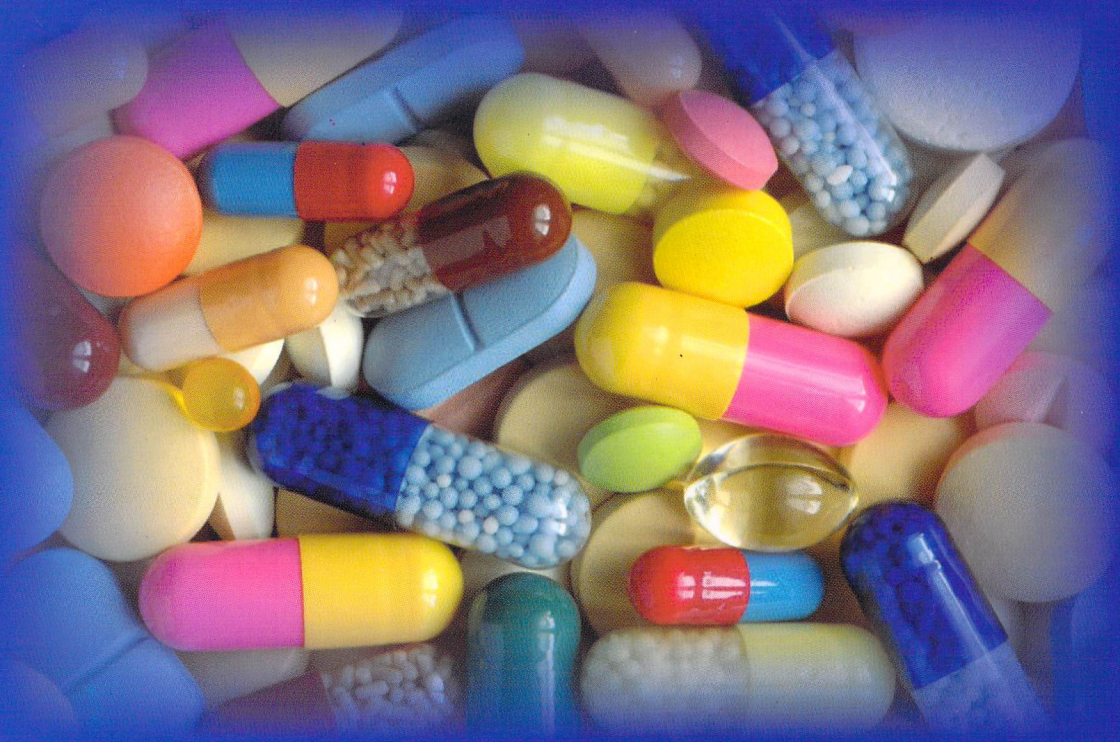
Pharmacology



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Part 1

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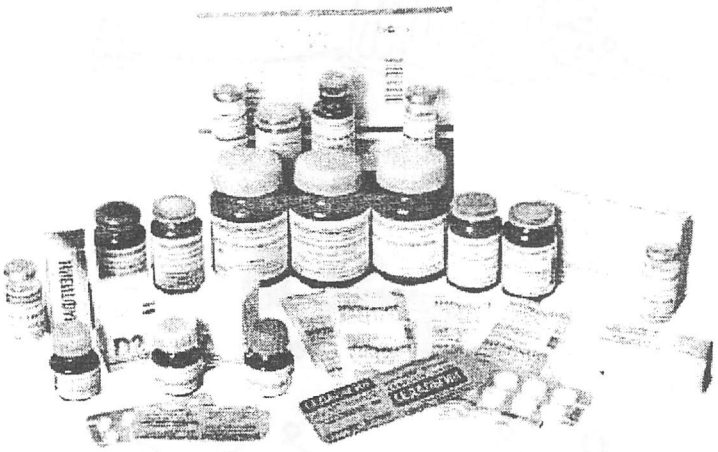
بسم الله الرحمن الرحيم

وَفِى أَنْفُسِكُمْ أَفَلَا تُبْصِرُونَ

«صدق الله العظيم»

General Pharmacology



PHARMACOLOGY

NB) The following scheme is used in discussion of a drug

Name Of The Drug

1- ***Definition***
2- ***Pharmacokinetics*** = What the BODY does to the DRUG = A. D. M. E.
   a- Absorption: Oral and/or Other
   b- Distribution: Binding to plasma proteins, Blood Brain Barrie & Placental barrier.
   c- Metabolism: Hepatic and/or Other
   d- Excretion: Renal and/or Other e.g. Milk
3- ***Pharmacodynamics*** = What the DRUG does to the BODY
   a- Mechanism of action
   b- Pharmacological actions:
      - Desirable = Therapeutic effects = Uses
      - Undesirable = Adverse effects = Side effects and toxicity
4- ***Pharmacotherapeutics***:
   a- Therapeutic uses = Indications
   b- Dosage
5- ***Side effects and toxicity***:
   a- Manifestations b- Management
6- ***Contraindications***
7- ***Drug interactions***.

PHARMACODYNAMICS

*(What the **DRUG** does to the **BODY**)*

⇒This science deals with ***Mechanism*** & pharmacological ***Actions*** of drugs.

⇒Drugs are chemical substances that modify (↑ or ↓) already present cell function but do not create a new one. However, genetic engineering and gene therapy may change this concept.

* *Types of Drug Action:*

1- *Local or Topical Action*:

a- NO Absorption from site of administration → NO Distribution → NO Systemic actions.
b- The drug acts at site of application.
c- *Examples* : Most of eye & ear drops, intra-articular injections & skin ointment.

2- *Systemic or General Action*:

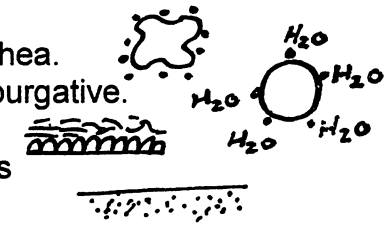
a- The drug is absorbed and distributed from site of administration.
b- *Examples* : Oral aspirin, Subcutaneous (SC) adrenaline & Sublingual (SL) isoprenaline.

3- *Reflex or Remote Action*:

a- The drug acts at a site to provoke an effect away from its site of action.
b- *Examples* : SC Camphor → Irritation → Reflex ↑ Respiratory center = Reflex Analeptic.

* Mechanism of Drug Action:

1- Physical:



a- Adsorption: Kaolin & Activated charcoal in diarrhea.
b- Osmotic: Mannitol as a diuretic & $MgSO_4$ as a purgative.
c- Demulcent: Liquorice as an anti-tussive.
d- Astringent: Tannic acid mouth wash in gingivitis

2- Chemical:

a- Neutralization:
  i- $NaHCO_3$ (Antacid) + HCl (Gastric acid) in treatment of hyperacidity.
  ii- Protamine sulfate (Basic) + Heparin (Acid) → Chemical antagonism.

b- Chelation: Organic compound + Heavy metal → Non-toxic easy excreted complex.
  i- Dimercaprol (British Anti-Lewisite or BAL) for Mercury (Hg), Arsenic (As) & Antimony (Sb)
  ii- Sodium Edetate for Calcium (Ca^{+2}).
  iii- d.Peniciilamine for Copper (Cu^{+2}).
  iv- Desferrioxamine for ferric iron (Fe^{+3}).

3- Interference with Cell Division: Anti-cancer drugs e.g. Nitrogen mustard.

4- Interference with Metabolic Pathway: Sulfonamides compete with PABA in bacteria → ↓ Synthesis of folic acid.

5- Inhibition of Enzymes: Physostigmine (↓ Cholinesterase), Aminophylline (↓ Phosphodiesterase, PDE) & Aspirin (↓ Cyclooxygenase, COX).

6- Action on Ion Channel:

a- Local anesthetics block Sodium (Na^+) channels.
b- Calcium channel blockers (CCB) e.g. Verapamil blocks L-type of voltage gated calcium channels of heart & blood vessels.
c- Some pharmacologists consider ion channels as an especial type of receptors.

7- Action on Receptors:

A Receptor is a chemo-sensitive & chemo-selective cellular macromolecule that reacts specifically with a Ligand (drug, transmitter or hormone) to produce a biological response:

$$\text{Drug} + \text{Receptor} \underset{(K_d)}{\overset{\text{Affinity } (K_a)}{\rightleftharpoons}} \text{Drug/Receptor Complex} \xrightarrow[\text{Intrinsic Activity}]{\text{Efficacy or}} \text{Response}$$

NB)

1- ***Affinity*** = Ability of a drug to fit onto a receptor to form Drug/Receptor complex.

2- ***Efficacy or Intrinsic Activity*** = Ability of D/R complex to evoke a response.

3- K_a = Association constant with the receptor

4- K_d = Dissociation constant from the receptor

* *Types of Receptors:*

1- Type I = Coupled directly to Ligand-gated Ion Channels:

a- A.Ch. + Nicotinic receptors (N_N & N_M) → ↑ Na^+ Channels → Depolarization.
b- GABA + $GABA_A$ receptors → ↑ Cl^- Influx → Hyperpolarization.

2- Type II = Coupled to G-protein:

a- Adrenaline + β-receptors → ↑ G_s-protein → ↑ Adenylate cyclase enzyme → ↑ cAMP
b- Adrenaline + α_2-receptors → ↑ G_i-protein → ↓ Adenylate cyclase enzyme → ↓ cAMP
c- A.Ch + $M_{1\&3}$-receptors → ↑ G_q-protein → ↑ Phospholipase C enzyme → ↑Inositol triphosphate (IP_3) & Di-acyl glycerol (DAG) → ↑ Ca^{+2} + Calmodulin → Response
d- A.Ch. + M_2 receptors → ↑ G-protein → ↑ K^+ channel → ↑ K^+ Efflux → Hyperpolarization.

3- Type III = Coupled to Kinase Activity:

Insulin receptors **(Tyrosine kinase)** & ANF receptors **(Guanylate cyclase)** activities.

4- Type IV = Modulation of DNA Transcription:

Thyroid & Steroid hormones + Intracellular receptors → DNA Transcription → mRNA → Change in protein synthesis.

NB) *The Amount of Response to Drug/Receptor Complex Depends on*:

A) Occupation Theory:

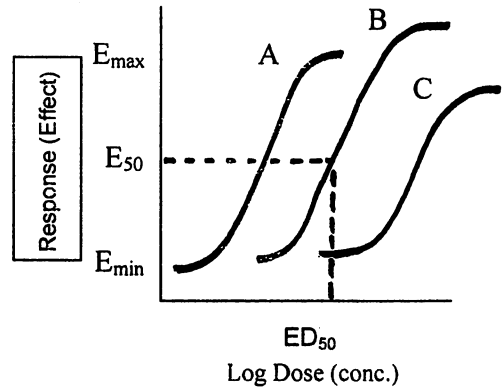
1- The amount of action ∝ Number of receptors occupied by the drug.
2- When a drug produces its Maximum effect; there will be some receptors remain free = Spare receptors.
3- However, the Efficacy of the drug is also an important factor.

B) Rate Theory of Paton:

1- The amount of action ∝ Rates of association (K_a) & dissociation (K_d) of D/R complex.
2- Higher rates = Higher activity.

* *Dose - Response Curve of Drugs:*

1- Relation between Log Dose and Response (Effect) of a drug
2- Useful to know ***Effects*** (responses): Minimal effect (E_{min}), Maximal Effect (E_{max}) & Submaximal effects e.g. 50% effect (E_{50})
3- Useful to know ***Doses*** that produce Minimal effect (ED_{min}), Maximal effect (ED_{max}) & Submaximal effect e.g. 50% effect (ED_{50})
4- Useful to ***compare*** drugs:
   a- **Efficacy (الفاعلية)** → Compare E_{max} (B>A>C)
   b- **Potency (القوة)** → Compare the doses that produce the same Submaximal effect (A>B>C)



5- Useful to determine the type of a ***blocker*** whether
   a- Competitive → Parallel shift to right (↓ Potency) with same E_{max} (Same efficacy)
   b- Non-competitive → Non-parallel shift to right (↓ Potency) with decreased E_{max} (↓ Efficacy)

* Types of Ligands

A) Stimulants = Agonists:

1- Affinity. 2- High intrinsic activity or efficacy → Stimulation of the receptor.
3- Rapid rates of association (K_a) & dissociation (K_d).
4- *Examples*: Adrenaline (α & β), A.Ch. (M & N) & Morphine (μ & κ).

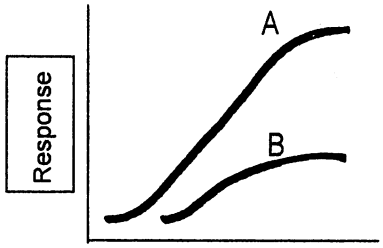
B) Blockers:

1- Antagonists:

a- Affinity. b- No = Zero efficacy → No dose/response curve
c- Slow dissociation from receptors.
d- Block the action of agonists.
e- *Examples* : Prazosin, propranolol, atropine & naloxone.

2- Partial Agonists = Dualists:

a- Affinity. b- Low intrinsic activity = Weak efficacy
→ Less maximum response (E_{max}) than agonists.
c- Moderate rates of association & dissociation.
d- Produces initial stimulation then block of the receptor
If used alone → Weak stimulation of the receptor → Weak response
If used in presence of an agonist → Block the action of the agonist.
e- *Examples* : Ergotamine (α + 5-HT), Oxprenolol (β), Nicotine (N_N) & Succinylcholine (N_M).

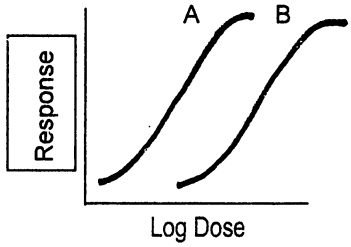


A = Full agonist B = Dualist

* Types of Block:

A) Competitive Block:

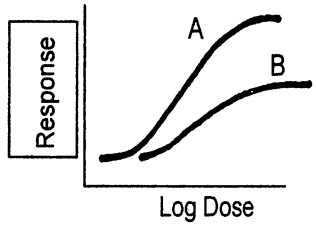
1- Antagonists bind ***REVERSIBLY*** with the receptors.
2- Antagonists can be ***DISPLACED*** by excess agonists → Surmountable
3- *PARALLEL* shift of the curve to the *RIGHT* → ↓ ***Potency***.
4- NO effect on the maximum response (E-max) = ***Same Efficacy***.
5- *Examples* : Propranolol, atropine & naloxone.



A = Agonist alone
B = Agonist + Competitive blocker

B) Non-Competitive Block:

1- Antagonist is NOT displaced by agonist → Non-surmountable
2- Non-Parallel shift of cure to the Right = ↓ ***Potency***.
3- Decrease maximum response (E-max) = ↓ ***Efficacy***.
4- *Types of Non-Competitive Block* :
a- **REVERSIBLE** :
i- The antagonist binds ***REVERSIBLY*** to the receptor.
ii- The block ends by the *Metabolism* of the blocker.
iii- Usually of *Short* duration of action.
iv- *Examples* : Nicotine LD & Succinylcholine.
b- **IRREVERSIBLE** :
i- The antagonist binds ***COVALENTLY*** to the receptor.
ii- The block ends by *Resynthesis* of new receptors.
iii- Usually of *Long* duration of action.
iv- *Examples* : Phenoxybenzamine & organophosphorus compounds.



A = Agonist alone
B = Agonist + Non-competitive blocker

NB) * *Types of Ligands:*

Characteristics	Stimulant = Agonist	Blocker	
		Antagonist	Partial Agonist = Dualist
1- Affinity	+ + +	+ + +	+ + +
2- Efficacy	+ + +	No = Zero	Moderate
3- K_a & K_d	Rapid	Slow	Moderate
4- Effect	Stimulation	Block	Stimulation then Block

NB) * *Types of Block:*

Competitive	Non-Competitive	
1- Blocker is displaced by excess agonist = Surmountable 2- Parallel shift of curve to right → ↓ Potency 3- Same E_{max} = Same Efficacy 4- Example: Atropine & Propranolol	1- Blocker is not displaced by excess agonist = Non-surmountable 2- Non-parallel shift of curve to the right → ↓ Potency 3- Decreased E_{max} → ↓ Efficacy 4- Types: Reversible & Irreversible	
	Reversible	Irreversible
	1- Block ends by metabolism of the blocker 2- Short acting 3- Example: Succinylcholine	1- Block ends by resynthesis of new receptors 2- Long acting 3- Example: Phenoxybenzamine

NB) Chronic Use of Drugs Affects the No. & Sensitivity of Receptors :
1- Long use of Agonists → ↓ No. & Sensitivity of Receptors → Down Regulation.
2- Long use of Antagonists or drugs that ↓ transmission → ↑ No. & Sensitivity of Receptors → Up Regulation.

Adverse & Toxic Effects of Drugs

I- Predictable Adverse Effects (Type A):

Related to the normal pharmacological actions of the drug (Drug effect):

1- Side effect
2- Secondary effect.
3- Over dose.
4- Supersensitivity.
5- Tolerance.
6- Drug dependence.
7- Drug interactions.
8- Iatrogenic diseases.
9- Teratogenicity.
10- Carcinogenicity.
11- Cytotoxicity.

II- Unpredictable Adverse Effects (Type B) :

Abnormal response to drugs due to abnormality in the patient (Patient effect). Not related to the normal pharmacological action of the drug:

1- Allergy (Hypersensitivity).
2- Idiosyncrasy (Pharmacogenetics).

Adverse & Toxic Effects of Drugs

1- *Side Effect:*

1- Unavoidable undesirable normal action produced by therapeutic dose of the drug.
2- Example: Dry mouth induced by atropine when used as antispasmodic.

2- *Secondary Effect:*

1- Bad effect consequent to normal therapeutic action of the drug.
2- Example: Oral broad spectrum antibiotics → ↓ Intestinal flora → ↓ Vit B & Vit K synthesis and superinfection.

3- *Over-dose:*

Exaggerated normal action due to high blood level of the drug either:
1- Single large dose: Insulin L.D. → Hypoglycemia
2- Accumulation of repeated doses: Digitalis (Long t ½)

4- *Supersensitivity (Intolerance):*

1- Exaggerated normal action in response to small therapeutic dose of the drug.
2- Either due to ↓ Elimination of the drug or up-regulation of receptors
3- Example: Hyperthyroidism → Supersensitivity to sympathomimetics.
4- Decrease the dose of the drug.

5- *Tolerance:*

- Decreased or failed response to drugs.
- Either ↑ dose of the drug or stop the drug for sometime.

* ***Types of Tolerance:***

A) Congenital (Inborn) Tolerance:

1-Racial: Ephedrine does NOT produce mydriasis in Negroes.
2- Species: Rabbits tolerate Atropine. They have excess atropine-esterase enzyme.
3- Individual (Biological) variations within any population

B) Acquired Tolerance:

1- Decreased response to drugs after their repeated (long) use e.g. Morphine & nitrates.
2- Types of Acquired Tolerance:
   a- *Cross Tolerance* between similar drugs e.g. Nicotine & Lobeline.
   b- *Tachyphylaxis* (Acute acquired tolerance) e.g. Ephedrine on blood pressure.
   c- *Bacterial resistance* to antimicrobials

* ***Mechanism of Acquired Tolerance:*** Change in Kinetics or Dynamics

1- ↓ Absorption: Long use of Ethanol → Atrophic gastritis
2- ↑ Metabolism: Phenobarbitone → HME inducer → ↑ Its own metabolism (Autoinduction)
3- ↑ Excretion
4- Down-regulation of receptors: Salbutamol → Down-regulation of β_2-receptors.
5- ↓ Endogenous substances: Morphine → ↓ Endogenous Endorphins & Enkephalins
6- Antibody formation e.g. Parathyroid hormone.

*** *Characteristics of Acquired Tolerance:***

1- It is a temporary process. Stop of the drug for sometime → Regain normal sensitivity.
2- Varies from one drug to another:
   a- Rapid with ephedrine & very slow with adrenaline
   b- No tolerance to digitalis or cocaine or diuretic effect of alcohol.
3- Does not affect all actions to the same extent: Long use of morphine → Rapid tolerance to analgesia & ↓ R.C. BUT NO tolerance to miosis or constipation.
4- It may affect therapeutic dose rather than the toxic dose → ↓ Therapeutic index.
5- Drug dependence (Habituation & Addiction) may follow tolerance.

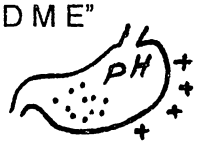
6- Drug Dependence:

1- **Habituation**:
   a- Psychic dependence.
   b- Sudden stop of the drug → Psychic craving for the drug
   c- Example: Xanthine beverages (Coffee & tea).
2- **Addiction**:
   a- Psychic and Physical dependence.
   b- Sudden stop of the drug → Withdrawal (Abstinence) syndrome → Usually the reverse of what the addicting agent does.
   c- Example: Amphetamine, Morphine, Ethanol, etc.

7- Drug Interactions:

A) Pharmacokinetic Interactions: "A D M E"

1- *Absorption*:



a- Motility:
   - Metoclopramide ↑ Gastric emptying → ↑ Abs. of Paracetamol but ↓ Abs. of digoxin
   - Atropine ↓ Gastric emptying → The reverse
b- pH:
   - Acid stomach → ↑ Absorption of weak acid drugs e.g. Aspirin and barbiturates
   - Alkaline intestine → ↑ Abs. of weak alkaline drugs e.g. Ephedrine & amphetamine
c- Content:
   - Tetracyclines chelate → Ca (Milk), Mg, Al, & ferrous iron
   - Activated charcoal → Adsorbs drugs } ↓ Absorption of other drugs e.g. Digitalis &Oral
   - Cholestyramine → Binds drugs } Hypoglycemics & Oral Anticoagulants

2- *Distribution*: Aspirin displaces oral anticoagulants & Oral hypoglycemics from their plasma binding sites → ↑ Their activity.

3- *Metabolism*:

a- HME inducers e.g. Phenobarbitone & Phenytoin → ↑ Metabolism of other drugs
b- HME inhibitors e.g. Estrogen & Cimetidine → ↓ Metabolism of other drugs

4- *Excretion*:

a- Probenecid → ↓ Active renal tubular excretion of Penicillin & Frusemide.
b- Alkalinization of urine ($NaHCO_3$) → ↑ Excretion of weak acid drugs e.g. Aspirin
c- Acidification of urine (NH_4Cl) → ↑ Excretion of weak base drugs e.g. Ephedrine

B) Pharmacodynamic Interactions:

I- Addition (Summation):

1- Active drug + Active drug → Algebraic sum of activity (1 + 1 = 2). Use ½ dose of each drug.
2- Example : A.Ch + Histamine on intestinal contractility.

II- Synergism:

1- Active drug + Active drug → More than algebraic sum of activity (1+1 = > 2).↓ Dose Of both.
2- Examples:
   a- Ethanol + Barbiturates or Chloral hydrate or Morphine → Severe ↓↓↓ CNS.
   b- d-Tubocurarine + Ether or Streptomycin → Severe muscle paralysis.

III- Potentiation:

1- Inactive drug (inert) increases the activity of Active Drug (0+1 = > 1). ↓ Dose of active drug.
2- Examples:
   a- Physostigmine (Anticholinesterase) potentiates A.Ch.
   b- Barbiturates (NOT analgesic) potentiate the analgesic effect of Aspirin.

IV- Antagonism:

1- Chemical:

a- Neutralization (Acid + Base): $Heparin^-$ + $Protamine^+$ sulfate.
- HCl + Sodium bicarbonate.

b- Chelation : Dimercaprol + Arsenic (As), Antimony (Sb) and Mercury (Hg).

2- Physiological:

a- 2 Agonists + 2 Receptors + 2 Opposing actions.
b- Example: Adrenaline (β_2) + Histamine (H_1) on bronchi.

3- Pharmacological:

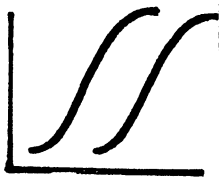
1- Pharmacokinetic Antagonism:

a- Absorption: Cholestyramine ↓ Absorption of Digoxin.
b- Metabolism: Phenobarbitone ↑ Metabolism of Warfarin.
c- Excretion: $NaHCO_3$ ↑ Excretion of Salicylates and Barbiturates.

2- Pharmacodynamic Antagonism: One Agonist + One Blocker + One Receptor.

a- *Competitive*: Excess Agonist CAN displace the Antagonist → *Surmountable*

i- A.Ch	+	Atropine	on M-receptors.
ii- Salbutamol	+	Propranolol	on β-receptors.
iii- Morphine	+	Naloxone	on Opiate receptors.



b- Non-Competitive: Excess Agonist can NOT displace Antagonist → *Non-Surmountable*

i- *Reversible*: The block ends by metabolism of the antagonist.
- Nicotine LD and Succinylcholine.

ii- *Irreversible*: The block ends by resynthesis of new receptor or enzyme.
- Organophosphorus. - Phenoxybenzamine. - M.A.O. Inhibitors.

V- Reversal:

1- A.Ch LD	+	Atropine	on Bl.p.
2- Adrenaline	+	Phentolamine	on Bl.p.
3- Reserpine	+	MAOI	on Bl.p. & C.N.S.

8- Iatrogenic Disease:

1- Drug-induced disease.
2- Examples: Large dose of Reserpine & Chlorpromazine → Iatrogenic Parkinsonism
Large dose of Cortisol → Iatrogenic Cushing's disease

9- Teratogenicity (Dysmorphogenesis):

1- Drug-induced fetal malformations. Especially when drugs are taken during the first trimester (First 3 months of pregnancy).
2- Examples:
a- Thalidomide → Phocomelia (Absent limbs)
b- Phenytoin → Hare lip and cleft palate
c- Aspirin → Cardiac septal defects
d- Tetracyclines → Teeth & Bone.

10- Carcinogenicity: Tobacco smoking → Bronchogenic carcinoma.

11- Cytotoxic Effects:

a- Cardio-toxicity: *Halothane*, Chloroform, Tartar emetic & Emetine HCl.
b- Hepato-toxicity: *Halothane*, Chloroform & *Paracetamol*.
c- Nephro-toxicity: *N.S.A.I.D.*, Aminoglycosides (Gentamicin) & Sulfonamides.
d- Neuro-toxicity: Streptomycin → 8th Cranial nerve damage.
e- Bone marrow inhibition (Blood dyscrasias): Chloramphenicol & Anti-thyroid drugs

12- Allergy (Hypersensitivity):

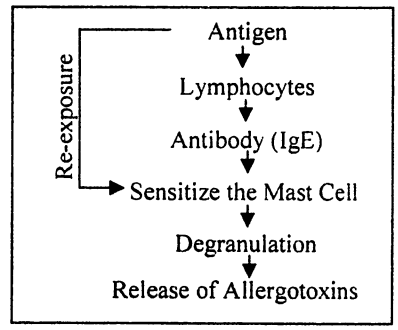
1- Unpredictable abnormal response to drugs due to antigen/antibody reaction.
2- The drug itself or its metabolites may act as an antigen or a hapten.
3- Allergy: - NOT all patients - NOT all drugs - NOT first exposure
- NOT dose dependent - NOT reuse the drug again
4- Cross allergy between related drugs e.g. Penicillins & Cephalosporins.

*** Types of Allergy:**

A) Type I (Immediate, Anaphylactic or IgE mediated):

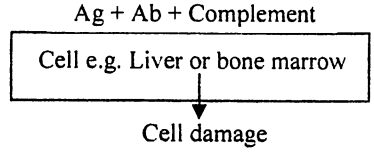
a- Antigen/Antibody (IgE) reaction on Mast cell → Degranulation → Release of allergotoxins e.g. Histamine

b- Manifestations: fever, rash, urticaria, photosensitivity, conjunctivitis, rhinitis, angio-edema, bronchial asthma, G.I.T. disturbances & even anaphylactic shock.

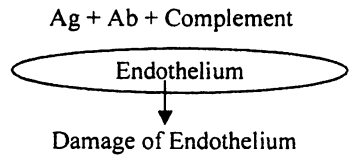


B) Type II (Auto-allergy, Cytotoxic or Cytolytic):

a- Antigen + Antibody (IgG & IgM) + Complement on a cell → Cell damage
b- Example: α-Methyldopa → Hepatotoxicity, hemolysis and bone marrow inhibition



C) Type III (Arthus Reaction):



a- Antigen + Antibody (IgG) + Complement on endothelial cell → Damage of endothelium.
b- Manifestations : Vasculitis & Serum sickness

D) Type IV (Delayed or Cell Mediated):

a- Antigen + Sensitized T-lymphocyte → Inflammation
b- Manifestation: Contact dermatitis.

E) Type V (Stimulatory Reaction): Formation of LATS → Hyperthyroidism.

13- Idiosyncrasy (Pharmacogenetics):

1- Unpredictable abnormal response due to genetic abnormality.
2- Occurs on first exposure.
3- Examples:
   a- *Hemolytic anemia* in patients with *Favism* (Glucose-6-Phosphate-Dehydrogenase enzyme deficiency) induced by: *Primaquine*, aspirin & sulfonamides.
   b- *Succinylcholine apnea* in patients with abnormal Pseudo-Ch.E. activity.
   c- *Malignant hyperthermia* induced by Succinylcholine & Halothane
   d- *Acute porphyria* in patients with acute intermittent porphyria induced by barbiturates due to ↑ of delta-amino-laevulinic acid synthetase enzyme.
   e- *Slow & Rapid Acetylators* of Isoniazide:
      - Slow Acetylators → Accumulation of Isoniazide # Vit B_6 → Peripheral neuritis
      - Rapid Acetylator → Accumulation of Acetyl-Isoniazide → Hepatotoxic.
   f- *↑I.O.P.* induced by Cortisol eye drops.

Doses of Drugs (Posology)

1- Therapeutic Dose: Average dose calculated for an Adult, Male, 20-60 year old & 70 Kg body weight.

2- Initial Dos; Initial large dose aiming to reach the therapeutic plasma concentration

3- Maintenance Dose: Small daily dose required to replace eliminated drug from the body to maintain the achieved therapeutic plasma concentration.

4- Maximal Tolerated Dose; Highest dose without toxic effects.

5- Lethal or Fatal Dose: Dose that kill the patient or an experimental animal

6- *Therapeutic Index:*
   a- Ratio = LD_{50} / ED_{50}
      - LD_{50} = Lethal dose in 50% of animals
      - ED_{50} = Effective dose in 50% of animals
   b- A good guide to determine & compare ***SAFETY*** of drugs
   c- The Higher the therapeutic index → The Safer the drug
   d- Valid only when dose/response curves for effectiveness & toxicity are parallel

7- Standard Margin of Safety (SMS):
   a- Percentage by which ED_{99} must be increased to reach LD_1.
   b- SMS = [(LD_1/ED_{99}) – 1] X 100
   c- Useful when dose/response curves for effectiveness & toxicity are not parallel.

Factors Affecting The Dose & Action of Drugs

1- Biological Variations	2- Age	3- Weight & Surface area	
4- Sex	5- Route & Time of administration		6- Cummulation
7- Psychology	8- Pathology	9- Idiosyncrasy	10- Allergy
11- Supersensitivity	12- Tolerance	13- Drug interactions	

1- Biological Variations: → Range of dose

Start by minimal effective dose then increase the dose gradually as needed.

2- Age: → Decrease the dose in extremities of age

1- Geriatrics (Elderly > 60 years):

a- They have exhausted drug-elimination mechanisms (metabolism & excretion).
b- Use 2/3 or 3/4 of the adult dose.

2-Pediatrics (Young < 20 years):

a- They have immature drug-elimination mechanisms (metabolism & excretion).
b- Calculate the dose by:
- **Infant** (< 1 year) dose (**Clark's Formula**) = Adult dose X (Weight of infant in Pounds/150)
- **Child** (1 – 12 year) dose (**Young's Formula**) = Adult dose X [Age in years / (Age + 12)]
  or (**Dilling's Formula**) = Adult Dose X (Age in Years / 20)

3- Body Weight & Surface Area:

1- Skeletal muscle weight is more important than fat or edema.
2- Surface area is more accurate in calculating doses for children & infants.

4- Sex:

1- Males need higher doses than females:
   a- Males have bulky muscle tissue & Androgens (HME Inducers)
   b- Females have bulky fat tissue & Estrogen (HME Inhibitor)

2- Some drugs are contraindicated in Females during physiological periods:
   a- *Menstruation*: Aspirin & Cathartics → ↑ Bleeding
   b- *Pregnancy*: Sex hormones, Oxytocics (Ergotamine) & Teratogens (Phenytoin)
   c- *Labor*: Barbiturates & Morphine → Neonatal asphyxia
   d- *Lactation*: Drugs excreted in milk eg Purgatives, Tetracyclines & Chloramphenicol

5- Route & Time Of Administration:

1- Affect the dose: usually I.V. dose < Oral dose

2- Affect the effect:

Mg SO_4
- Orally
  - After meal → No effect
  - Empty stomach
    - 4 g → Cholagogue
    - 15 g → Saline purgative
- I.V. → ↓ CNS, ↓ Smooth muscle, ↓ Skeletal muscle & ↓ Cardiac muscle
- Retention Enema → Dehydrating agent e.g. in brain edema

3- If drug is irritant → Use after meals
4- If drug is sedative → Use at bed time

6- *Cumulation:*

1- Occurs with zero-order kinetics when the rate of intake > rate of elimination.
2- Examples: Digitalis, Aspirin L.D., Phenytoin L.D. & Ethanol L.D.
3- To avoid cumulation either ↓ The dose or ↓ Frequency of administration.

7- *Psychological Effect:*

1- Some patients improve by Psychological (Suggestion) rather than Pharmacological effect of the drug (Placebo effect).
2- Placebo (Dummy medication) is an inert substance (Lactose, starch, etc.) used in a dosage form (Tablet, capsule, etc). Useful in:
   a- Treatment of patients by psychological suggestion
   b- As a comparison when testing new drugs

8- *Pathological Condition:*

1- Some drugs act *ONLY* in presence of disease:
   a- Aspirin acts as an antipyretic ONLY in fever
   b- Digitalis acts as a diuretic ONLY in heart failure
2- Pathology may cause *supersensitivity*:
   a- Adrenaline in thyrotoxicosis
   b- β-Blockers in bronchial asthma
3- Pathology may affect drug *kinetics*: Achlorhydria → ↓ Intrinsic factor → ↓ Absorption of Vit B-12 → Pernicious anemia.

9- *Allergy (Hypersensitivity)* → Abnormal response

10- *Idiosyncrasy (Pharmacogenetics)* → Abnormal response

11- *Supersensitivity (Intolerance)* → ↓ Dose of the drug

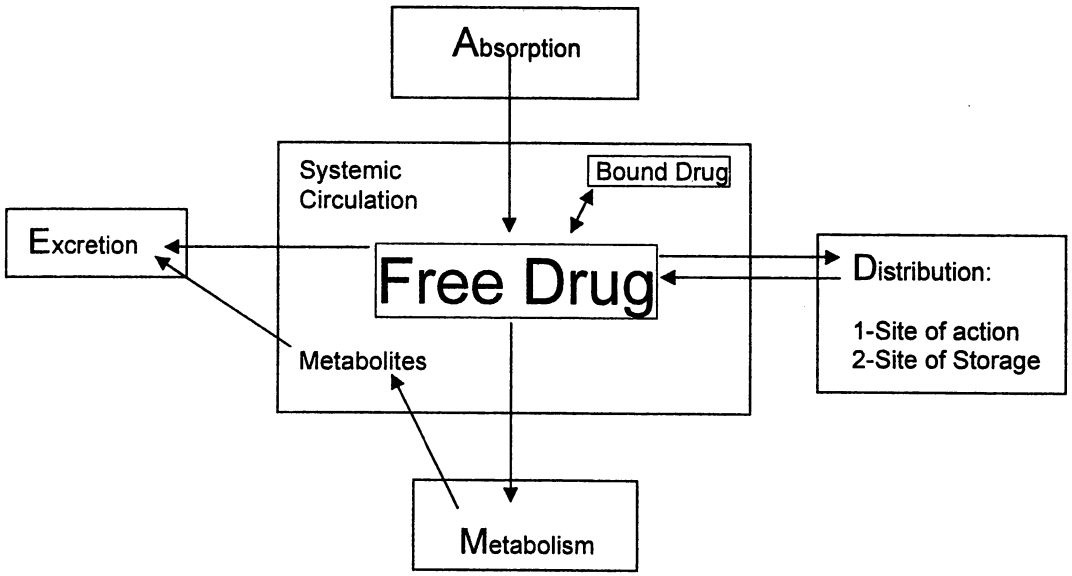
12- *Tolerance* → ↑ Dose of the drug

13- *Drug interactions* → Summation, Synergism, Antagonism & Reversal.

PHARMACOKINETICS

(What the Body dose to the Drug?)

Absorption, Distribution, Metabolism & Excretion (ADME)

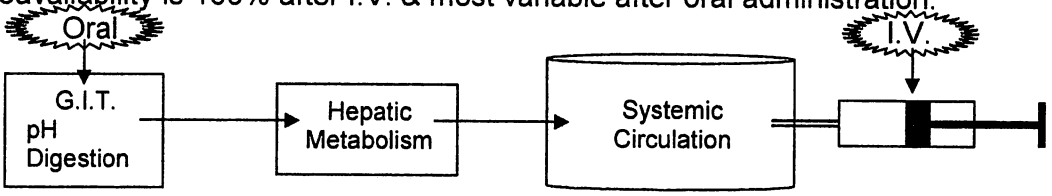


The study of pharmacokinetics is important to design a proper dosage schedule (Dose, route, frequency of administration) and to determine the drug's bioavailability.

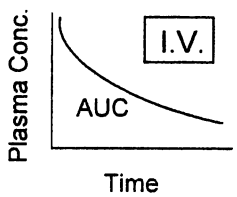
* *Bioavailability:*

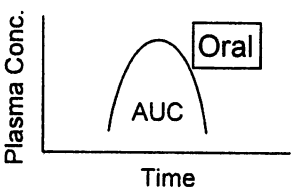
1- The fraction (%) of administered drug that reaches the systemic circulation in an unchanged form.

2- Bioavailability is 100% after I.V. & most variable after oral administration.



3- Bioavailability of a Route = $\frac{\text{Area under the curve (AUC) of the route}}{\text{Area under the curve (AUC) of I.V. route}} \times 100$

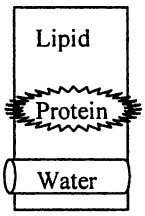




Transmembrane Movement of Drugs
Passage of Drugs Across Biological Membranes

Cell membrane is formed mainly of bimolecular LIPID sheet, interrupted by protein macromolecules (receptors, carriers, etc.), water-filled pores & ion channels.

* *Types of Passage of drugs:*



A) Passive Transfer :

1- Simple Diffusion:

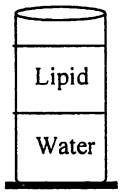
a- Mostly across the LIPID phase of cell membrane.
b- Water & water-soluble small M.W. drugs pass across the water-filled pores.

*** *Characteristics:***

1- Along concentration gradient. 2- **NO** carrier. 3- **NO** energy.

*** *Factors & Forces:***

1-Gradient (Concentration of drugs & Electric of ions):
Higher gradient = Higher rate of passage across the membrane.
2-Molecular weight & size: The smaller is the faster.
3-Solubility in water is a must.
4-Oil (lipid) / Water (O/W) partition coefficient. The higher is the better.
5-Ionization:



	A	B
	9	2
	/	/
	1	8
	✓	x

a- It depends upon pH of the medium & pKa of the drug.
(pKa = Dissociation constant of drug = pH at which 50% of drug is ionized).
b- Low Ionization = High lipid solubility = Better passage.
c- Degree of ionization is determined by the **Henderson Hasselbalch equation** :
-For weak ACID drugs: pKa = pH + log **Un**ionized form / **I**onized form.
-For weak BASE drugs: pKa = pH = Log **I**onized form / **Un**ionized form.

*** *Effect of pH on Oral Absorption & Renal Excretion of Drugs*** :

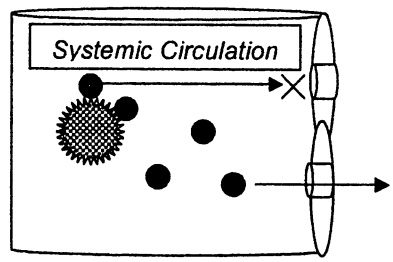
1- For weak base and acid drugs:
a- The unionized (non-polar) form is lipid soluble and easily absorbed.
b- Ionized (polar) form of drugs is lipid insoluble and not easily absorbed but easily excreted.
2- According to Henderson-Hasselbalch equation :
a- For weak acids : pKa = pH + Log **UN**ionized / Ionized drug.
Weak acid drugs are more unionized in acid & more ionized in alkaline media.
b- For weak bases: pKa = pH + Log Ionized / **UN**ionized drug.
Weak base drugs are more unionized in alkaline & more ionized in acid media.
3- Weak acid drugs e.g. Aspirin and Barbiturates:
a- Better absorbed in acid medium e.g. Stomach.
b- Alkalinization of urine by sodium or potassium acetate, bicarbonate, benzoate or citrate → ↑ Their urinary excretion.
c- Acidification of urine → ↓ Their urinary excretion.
4- Weak base drugs e.g. Ephedrine & Amphetamine :
a- Better absorbed in alkaline medium e.g. Intestine.
b- Alkalinization of urine → ↓ Their urinary excretion.
c- Acidification of urine by ammonium chloride or ascorbic acid → ↑ Their urinary excretion.

2- *Filtration:*

Passage of drugs through capillary endothelium & Glomeruli

*** *Characteristics*:**

1- ***Along*** hydrostatic and osmotic gradients
2- No carrier
3- No energy

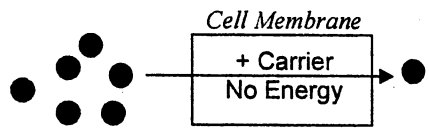


*** *Factors & Forces*:**

1- Molecular weight < 500
2- Not bound to plasma proteins
3- Hydrostatic and osmotic gradients
4- Blood flow

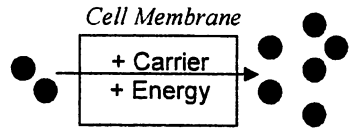
B) *Special Transfer:*

1- *Facilitated Diffusion:*



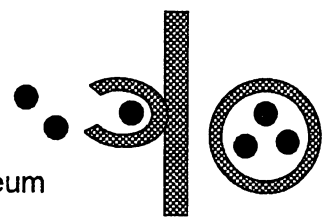
1- ***Along*** concentration gradient
2- Needs ***Carrier*** → Site for Saturation & Competition (Interaction)
3- ***No*** energy
4- *Example*: Glucose uptake

2- *Active Transport:*



1- ***Against*** concentration gradient
2- Needs ***Carrier*** → Site for Saturation & Competition (Interaction)
3- ***Energy*** & ***Enzymes***
4- *Example*: Na^+/K^+ pump & Renal tubular excretion of penicillins

3- *Pinocytosis (Cell Drinking):*



1- Energy dependent
2- Example: Absorption of Vit B_{12} + Intrinsic factor by terminal ileum

Characteristics	Simple Diffusion	Facilitated Diffusion	Active Transport
1- Gradient:	Along	Along	***Against***
2- Carrier:	NO	***Yes***	***Yes***
3- Saturation & competition:	NO	***Yes***	***Yes***
4- Energy:	NO	NO	***Yes***
5- Example:	Lipid soluble drugs	Glucose	Na^+/K^+ pump

I- Absorption

Transfer of drugs from their site of administration to the systemic circulation

*Factors Affecting Absorption:

A) Factors Related to the Patient:

1-*Route of Administration*: I.V. > I.M. > S.C. > Oral > Skin

2-*Absorbing Surface*:
- a-Vascularity: Alveoli > Skeletal muscle > Subcutaneous
- b-Surface area: Alveoli > Intestine > Stomach
- c-State of health: Diarrhea & mal-absorption → ↓↓ Oral absorption

3-*Systemic circulation*: Shock & Heart failure → ↓↓ Absorption

4-*Specific factors*: Intrinsic factor for Vit B-12

5-*Presence of other drugs*:
- a-Adrenaline S.C. → V.C. → ↓↓ Absorption of Local anesthetics → Long duration of action
- b-Milk (Calcium) → ↓↓ Oral absorption of Tetracyclines (Antibiotic)

B) Factors Related to the Drug:

1- *Water and lipid solubility*:
- a- Drugs MUST be Water soluble as well as Lipid soluble.
- b- Drugs must be completely dissolved in water to be absorbed.
  Drugs insoluble in water e.g. Barium chloride ($BaCl_2$) are NOT absorbed.
- c- More lipid solubility → High Lipid/Water partition coefficient → Better absorption

2- *Ionization*:
- a- Non-ionized → More lipid soluble → Better absorption
- b- Depends on pKa of the drug & pH of the medium.
- c- Quaternary ammonium compounds → Ionized → Poor absorption
- d- Tertiary amines → Non-ionized → Better absorption.
- e- Streptomycin has high pKa → Always ionized → Not absorbed
- f- Sulfaguanidine → Not ionized yet → Not lipid soluble → Poor absorption.

3- *Valency*: Ferrous iron (Fe^{2+}) > Ferric Iron (Fe^{3+})

4- *Nature*: Inorganic (small molecules) > Organic (Big molecules)

5- *Pharmaceutical Preparation*:
- a- Dosage form: Solution > Suspension > Tablet
- b- Shape & size of particles and rates of disintegration & dissolution of tables:
  Rapid with paracetamol & propranolol *BUT* slow with digoxin
- c- Excepient (Filler): $CaCO_3$ & Ca Phosphate → ↓ Absorption of Tetracyclines

Routes of Administration

Enteral	Others
1- Buccal e.g. Sublingual 2- Oral 3- Rectal	1- Parenteral e.g. Injection 2- Inhalation 3- Topical

NB) Effect Of Administered Drug:

1-Systemic (General): If drug is absorbed and distributed

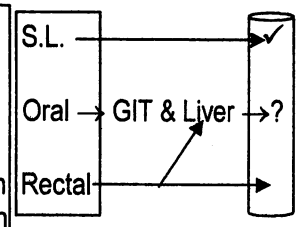
2-Local (Topical): If drug is not absorbed nor distributed

Enteral Route

1-Sublingual → Absorbed directly →Systemic circulation → ***Good*** Bioavailability.

2-Oral → Stomach & Intestine → pH changes & enzymes → Portal circulation
→ Liver metabolism → Systemic circulation → ***Most variable*** Bioavailability.

3-Rectal (Suppository) →
a-Upper rectum → Portal circulation → Liver metabolism → Systemic circulation
b-Lower rectum ——————→ Systemic circulation

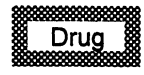


1- Oral Route

A) Characteristics:

1- Suitable:
- a- Small amount or volume
- b- Palatable: If bad taste →
  - - Dilute with milk or fruit juice
  - - Use sugar coated or effervescent form
- b- Non-irritant: If Mild irritant →
  - - Take after meal
  - - Use enteric coated form: Covered with acid resistant coat

NB) Enteric Coated Tablet
e.g. Na Salicylate



Acid resistant coat e.g. Shellac

2- Stable: pH changes, digestive enzymes & hepatic enzymes.

3- Absorbable if used for systemic effect

B) Advantages: Convenient (Safe, easy & economic)

C) Disadvantages:

1-NOT in emergency → Delayed onset

2-NOT in uncooperative patients e.g. coma, insane or very young

3-NOT in vomiting or severe diarrhea

4-NOT in very irritant drugs e.g. Emetine HCl (Anti-amebic)

5-NOT absorbed drugs when systemic effect is wanted (Streptomycin in TB)

6-NOT for drugs with extensive First Pass Effect (Metabolism):
- a-pH changes: Benzyl penicillin is destroyed by gastric acidity
- b-Digestive enzymes: Insulin
- c-Hepatic enzymes: Nitroglycerin (Anti-anginal)

D) Factors Affecting Oral Absorption:

1- **S**tate of Health of G.I.T. Mucosa e.g. Mal-absorption Syndrome.
2- **S**pecific Factors e.g. Intrinsic Factor for Vit B_{12} Absorption.

3- **G**astric Emptying:
   a- Metoclopramide (Primperan, Anti-emetic) → ↑Emptying →
      - ↑ Absorption of Paracetamol (Rapid rates of Disintegration & Dissolution).
      - ↓ Absorption of Digoxin (Slow rate of Disintegration & Dissolution)
   b- Atropine → ↓ Emptying → The REVERSE Effects.
4- **G**ut Motility: Marked alterations (e.g. Morphine) → ↓ Absorption.

5- **p**H
   a- Gastric Acidity → ↑ Absorption of Salicylates & Barbiturates
   b- Intestinal Alkalinity → ↑ Absorption of Ephedrine & Amphetamine.
6- **P**resence of FOOD & Other DRUGS:
   a- Bad → Food dilutes Drugs & may compete with them for absorption e.g. aminoacids compete for the same carrier of L-DOPA
   b- Good → with IRRITANT drugs e.g. aspirin & iron.
   c- Milk (Ca^{2+}) & Anti-acids → Interfere with Tetracycline absorption.
   d- Tea (Tannic Acid) & Tetracycline → ↓ Iron absorption.
   e- Cholestyramine & Activated Charcoal → ↓ Absorption of Most Drugs.

7- **First Pass Effect (Pre-Systemic Metabolism):** ↓ Bioavailability
   a- Gut First Pass Effect:
      - Gastric Acidity: Benzyl Penicillin.
      - Digestive Enzymes: Insulin & Pituitary hormones
      - Mucosal enzymes: Tyramine, L-DOPA, α-Methyldopa & Chlorpromazine
   c- Hepatic First Pass Effect:
      - Extensive: Nitroglycerine, Lidocaine & Natural sex hormones.
      - Partial: Propranolol & Morphine.
      - Minimal: Atenolol, Nadolol & Barbitone.
   d- How to OVERCOME Hepatic First Pass Metabolism?
      - Increase the oral dose of the drug e.g. Morphine & Propranolol
      - Use other routes (NOT ORAL) e.g. Sublingual "Nitroglycerine".

8- **F**actors related to the **DRUG** e.g. Lipid Solubility.

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2- *Sublingual* (Pellet or Linguat)

**Example:* Isoprenaline & Nitroglycerine.

**Advantages:*

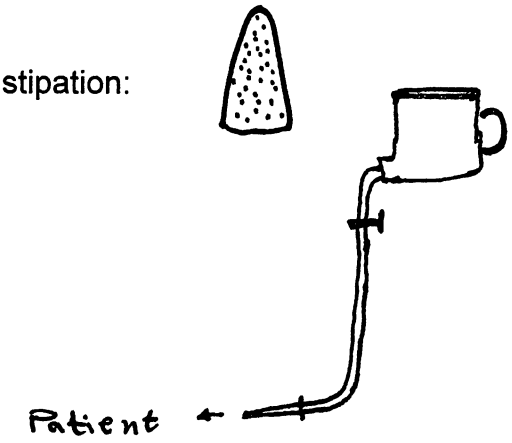
1- Easy.
2- Escape gut and hepatic first pass effect → Good bioavailability.
3- Rapid onset.
4- Proper control of dose by either spitting or swallowing excess of the drug.

3- Rectal:

A) Either:

1- ***Solid (Suppository)***: Drug (Aminophylline) in a cone of gelatin or cocoa butter.

2- ***Fluid (Enema)***:



a- Evacuant (Cleansing) enema e.g. for constipation:
- -Large volume (1 liter)
- -High head pressure
- -Mild irritant (chamomile)

b- *Retention enema* e.g. Nutrient:
- -Small volume (1/4 liter)
- -Low head pressure
- -Non-irritant

B) Advantages:

a- Escape gut & hepatic first pass effects
b- Useful in patients with vomiting
c- Useful in uncooperative patients e.g. coma & young children
d- Useful in mild irritant drugs e.g. aspirin and aminophylline
e- Useful in large volume drugs

Parenteral Routes

All drugs must be STERILE and PYROGEN-FREE

A)Subcutaneous Pellet Implantation:

Sterile pellet under the skin → Fibrosis → Slow absorption → Long duration e.g. some hormones (Contraceptives).

B)Intradermal Injection (I.D.): e.g. Sensitivity tests & Vaccinations.

C)Subcutaneous Injection (S.C.):

1-Drugs should be:
- a- Non-irritant
- b- Aqueous Solution or fine suspension.
- c- If irritant or oily → Inflammation

2-Absorption can by *Enhanced* by:
- a- Use a solution
- b- Massage of injection area
- c- Application of heat
- d- Add hyaluronidase enzyme

3-Absorption can be *Slowed* by:
- a- Use a suspension
- b- Application of cold
- c- Add adrenaline (V.C.) to local anesthetics
- d- Add gelatin to heparin

4- Hypodermoclysis: Injection of large volume S.C. e.g. Saline (Add hyaluronidase).

D) Intramuscular (I.M.):

1- Drugs can bye: Solution, suspension, oily, non-irritant or mild irritant.
2- Better absorption than S.C.
3- Some drugs (Diazepam & Phenytoin) → Bound to muscle proteins → Irregular absorption.

E) Intravenous (I.V.):

1- Either **SLOW** bolus injection or **Infusion** (Drip) method.

2- Water solution **ONLY**.

3- **Advantages**:
   a- 100% bioavailability } Useful in Emergencies
   b- Immediate onset }
   c- High plasma concentration
   d- Useful for Irritant & Large volume drugs

4- **Disadvantages**: MOST DANGEROUS ROUTE
   a- If Allergy → Anaphylactic shock
   b- If Very Irritant → Thrombophlebitis
   c- If Extravasation of irritant drug → Severe pain and inflammation
   d- If Rapid I.V. → Velocity reaction → Cardiac problems (Aminophylline)
   e- Pyrogenic reaction by phospho-lipo-protein of microorganisms
   f- Transmission of diseases e.g. Viral Hepatitis C & AIDS.

F) Other Injections:

1- Intra cardiac e.g. Adrenaline in cardiac resuscitation
2- Intra-umblical = I.V. in new born e.g. Lobeline in neonatal asphyxia
3-Intra-bone marrow = I.V.
4- Intra-arterial e.g. Angiography and cancer chemotherapy
5- Intra-peritoneal as substitute for Hemodialysis
6- Intra-thecal (CSF) e.g. spinal anesthesia, antibiotics in meningitis & Radiography
7- Intra-articular e.g. Steroids in osteoarthritis
8- Intra-cameral (Into aqueous humor)

Inhalation

1- Inhaled drugs may be the form of:
   a-Gas e.g. Oxygen & Nitrous oxide
   b-Vapor of Volatile liquid e.g. Halothane (General anesthesia)
   c-Solution e.g. Salbutamol (B_2-agonist in Bronchial asthma)
   d-Powder e.g. Di-sodium-cromoglycate (Mast cell stabilizer in Bronchial asthma)

2-Excellent absorption:
   a-Wide surface area
   b-High vascularity
   c-Thin porous membrane

Topical e.g. Skin

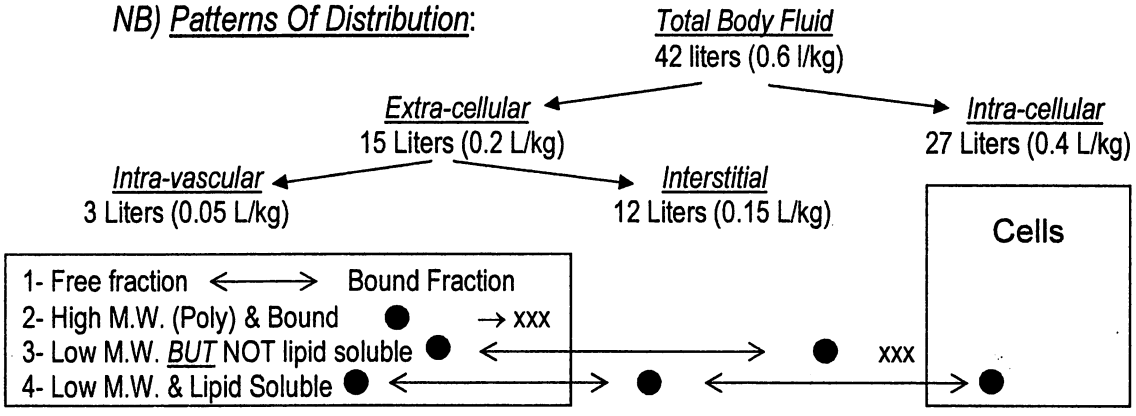
1-Usually → *Local effect*. However highly lipid soluble drugs can be absorbed from the skin.

2-Skin absorption can be *enhanced* by:
- a-Iontophoresis by the aid of galvanic electric current e.g. Methacholine in P.V.D.
- b-Inunction by the aid of rough rubbing.
- c-Transdermal Drug Delivery System (TDDS) e.g. Skin patch of nitroglycerine
  - Prolonged blood level with minimal fluctuations
  - Better patient compliance
  - Avoid gut & hepatic first pass effect

3-Usually skin absorption is not wanted and *harmful*:
- a-Estrogen hormone in females → Cancer breast.
- b-Cortisone in infants → Moon face.
- c-Insecticides → Toxicity.

Distribution

NB) Patterns Of Distribution:



A) Binding To Plasma Proteins:

1- A fraction of *Most* drugs binds *Reversibly* to plasma proteins.
2- *Albumin* is the major binding plasma protein.
3- The *Bound* fraction of the drug → *NOT* Active, *NOT* Filtered, *NOT* Metabolized & *NOT* Excreted → Depot Form. More binding = More Depot = Longer duration.
4- The *Free* fraction of the drug → Active, Metabolized & Excreted.
5- There equilibrium between the bound & the free fractions of the drug.
6- In cases of hypoproteinemia (Hypoalbuminemia) → ↑ Free fraction of drugs.
7- Drugs extensively bound to plasma proteins e.g. Thiopentone (I.V. Anesthesia) & Diazoxide (Arterio-dilator) have to be injected rather *Rapidly* I.V.
8- Drugs have specific binding sites on plasma proteins = Non-functioning receptors → Site for competition & drug interactions.
9- Site for *Drug Interactions*: Aspirin (NSAID), Phenytoin & Sulfa drugs displace:
   a- Oral Anti-coagulants e.g. Warfarin → Hemorrhage.
   b- Oral Hypoglycemics e.g. Tolbutamide → Hypoglycemia.
   c- Bilirubin in neonates → Jaundice & Kernictrus.

B) Patterns Of Distribution:

1- Intra-vascular (Single Compartment):

a- Drug is retained in the blood compartment.
b- Drugs that can NOT filtrate through capillary endothelium.
c- Examples High MW > 500 e.g. Polypeptides (Plasma proteins & Drugs bound to plasma proteins) & Polysaccharides (Heparin & Dextrans).

2- Extra-cellular (Two compartments = Intra-vascular + Interstitial):

a- Drugs that can filtrate (Small MW) but can NOT pass cell membrane (Not lipid soluble).
b- Quaternary ammonium compounds (Neostigmine), Mannitol, Na^+, Cl^- & SO_4.

3- All over the body (Multi-compartment = Intra + Extra-cellular):

a- Drugs that can filtrate (Small MW) & Can pass cell membrane (Lipid soluble).
b- Tertiary amines (Physostigmine), Alcohol, Aspirin & Barbiturates.

4- Tissue Reservoirs:

a- Hair: Arsenic
b- Thyroid: Iodine
c- Heart: Digitalis
d- Liver: Vit B_{12} & Chloroquine
e- Fat: Thiopentone
f- Bone: Ca^{2+}

5- Blood Brain Barriers:

a- Lipid cellular barrier composed of Brain Capillary Endothelium (Which lacks the water channels) and the adjacent Glial tissue.
b- Only lipid soluble Non-ionized drugs can pass B.B.B. along their concentration gradient.
c- Inflammation (Meningitis) increases permeability of B.B.B.
Penicillins can pass inflamed meninges but NOT normal ones.

6- Placental Barrier:

a- Lipid cellular barrier composed of Epithelium of Fetal Villi & Capillary endothelium.
b- Rich in enzymatic activity e.g. M.A.O.
c- Drugs that pass placental barrier may cause:
- During pregnancy → Teratogenicity e.g. Thalidomide & Tetracyclines
- During Labor → Neonatal asphyxia e.g. Morphine & Barbiturates.

C) Apparent Volume Of Distribution (Vd):

a- $Vd = \frac{\text{Total amount of the drug in the body (M)}}{\text{Plasma Concentration of the drug (C)}}$

b- Vd: Hypothetical volume at which the drug should be distributed (diluted) to attain the estimated plasma concentration of the drug.
c- Useful to estimate the amount of drug in the body (M) = (Vd) X (C)
d- Drugs highly bound to plasma proteins → Small Vd = Plasma volume
e- Drugs highly bound to Tissue proteins → High Vd > Total body fluids
- Slow clearance → Long elimination time → Long half life (t1/2).
- No need for dialysis in treatment of toxicity.

Metabolism (Biotransformation)

Chemical alteration of the drug *AIMING* to convert: ***Drugs*** (Active, Non-ionized & Lipid soluble) → ***Metabolite*** (Inactive, Ionized & water soluble) → ***Easily excreted*** in urine & bile.

* *Types of Metabolism:*

A) Phase-I (Non-Synthetic) → **Oxidation, Reduction & Hydrolysis**

1- Oxidation:

a- Ethyl alcohol → Acetaldehyde → Acetic acid → CO_2 + H_2O + Energy

b- Phenacetin (Active) → Paracetamol (Active)

2- Reduction:

- Chloral hydrate (Active) → Tri-chloro-ethanol (More active)

3- Hydrolysis:

a- Acetylcholine (Active) → Acetic acid + Choline (Inactive)

b- Di-acetyl-morphine (Heroin) → Acetic acid + Morphine (Active)

NB) Result of Phase-I Metabolism:

1- *Inactivation*: ***Active*** Drug → ***Inactive*** Metabolite
   a- Adrenaline & Noradrenaline → Vanil Mandilic Acid (VMA)
   b- Serotonin → 5-Hydroxy-Indol-Acetic Acid (HIAA)

2- *Activation*: ***Inactive*** Drug (***Prodrug***) → ***Active*** metabolite
   a- Imipramine (Inactive) → Desipramine (Active)
   b- Phenoxybenzamine (Inactive) → Ethylenimonium$^+$ (Active)

3- *Maintain Activation*: ***Active*** Drug → ***Active*** Metabolite
   a- Phenacetin (Active) → Paracetamol (Active)
   b- Diazepam (Active) → Nor-diazepam (Active)

4- *Toxification*: ***Drug*** → ***Toxic*** metabolite
   a- Methyl alcohol → Formaldehyde → Blindness
   b- Parathion & Malathion → Para-oxone & Mala-oxone → Toxic to insect & man

B) Phase-II (Synthetic, Conjugation):

- Usually leads to inactivation
- May lead to activation e.g. Morphine → Morphine-6-Glucoronoid (More active)

1- *Glucuronic acid* → Aspirin, Paracetamol, Morphine & Chloramphenicol.

2- *Acetic acid* (Acetylation) → Isoniazide, Sulfonamides & Hydralazine.

3- *Methylation* → Noradrenaline (→ Active Adrenaline) & Histamine.

4- *Glycine* → Aspirin

* *Site Of Biotransformation:*

1- *Organs:*

a- Liver (Hepatic) is the main site for biotransformation
b- Lung → Nicotine, Prostaglandins & Angiotensin (ACE).
c- Kidney → Vitamin D
d- G.I.T. & Gut flora → Tyramine & Histamine
e- Skin → Vitamin D
f- Plasma (Cholinesterase) → Succinylcholine

2- *Cellular Enzymes:*

	Microsomal	Non-Microsomal
1- Site:	Smooth endoplasmic reticulum	Cytoplasm, Mitochondria, etc.
2- Organs:	Mainly Hepatic	All organs
3- Phase-I:	Oxidation / Reduction (Cytochrome P-450)	Oxidation/Reduction & Hydrolysis
4- Phase-II:	Glucuronidation ONLY	All *Except* Glucuronic acid
5-Induction:	Inducible	NOT inducible

* *Factors Affecting Hepatic Microsomal Enzymes:*

A) Hepatic Microsomal Enzyme Inducers (Activators):

1- Examples: Phenobarbitone, Phenytoin, Phenylbutazone, Carbamazepine, Rifampicin, Gresiofulvin, Testosterone, Cortisol & Tobacco smoking.
2- They ↑ Metabolism of other drugs e.g. Oral anti-coagulants, Oral hypoglycemics & Oral contraceptives → ↓ Their duration of action.
3- They ↑ Their own metabolism (Auto-induction) → Tolerance.

B) Hepatic Microsomal Enzyme Inhibitors:

1- *Specific*: SKF-525, Estrogen, Progesterone, Cimetidine, Sodium valproate, Chloramphenicol, Erythromycin & Ciprofloxacin.

2- *Non-specific (General)*:

a- Hepato-toxic drugs: Carbon monoxide, Carbon tetrachloride & Ozone.
b- Drugs ↓ Hepatic blood flow: β-Blockers (Propranolol) & H_2-Blockers (Cimetidine)

C) Age:

1- ↓ H.M.E. Activity in extremities of age.
2- Premature neonate can *NOT* conjugate chloramphenicol → Fatal Grey Baby Syndrome.

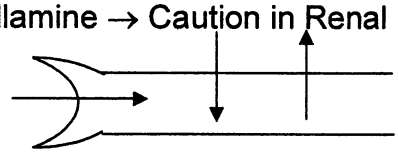
D) Liver disease, Starvation & Cancer → ↓ H.M.E. Activity

E) Genetic Abnormality (Idiosyncrasy): Favism & Abnormal Pseudo-Ch.E.

Excretion

A) Renal:

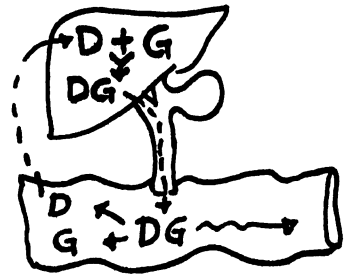
1- *Non-volatile* drugs and metabolites are excreted in the urine.
2- The clearance of *some drugs* depends mainly on renal excretion (Little or no metabolism) e.g. Atenolol, Nadolol, Barbitone & Gallamine → Caution in Renal patients.
3- Renal excretion is the *result* of glomerular filtration and active tubular secretion & reabsorption.



4- *Passive Glomerular filtration* for water soluble Non-bound drugs with M.W. < 500 e.g. Mannitol.
5- *Active Tubular Excretion* (Saturable & Site for competition & Drug Interaction):
   a- *Weak acid drugs* e.g. Penicillin, Frusemide, Uric acid & Probenecid.
      NB) Probenecid → ↓ Urinary excretion of Penicillin & Frusemide.
   b- *Weak base drugs* e.g. Digoxin & Quinidine
      NB) Quinidine → ↓ Renal clearance of Digoxin.
6- *Changes in urinary pH* → Affect excretion of weak Acid & Base drugs:
   a- Alkalinization of urine (Na or K Acetate, Bicarbonate or Citrate) →
      ↑ Renal excretion of weak Acid drugs e.g. Aspirin & Phenobarbitone
   b- Acidification of Urine (NH_4Cl or Ascorbic acid "Vit C") →
      ↑ Renal excretion of weak Base drugs e.g. Ephedrine & Amphetamine.

B) Lung → Gases (CO_2) & Volatile Liquids (Halothane)

C) Alimentary Tract:



1- *Saliva (pH = 8)*:
a- Drugs: Morphine & Aspirin
b- Elements: Iodide & Mercury.

2- *Stomach* → Morphine.

3- *Bile* → Intestine → Either:
a- Excreted in large intestine
b- Reabsorbed → Entero-Hepatic Circulation e.g. Morphine, Indomethacin, Sulindac, Digitoxin, Rifampicin, Thyroxin & Phenolphthalein.
c- Some anti-microbials are excreted in bile in an active form e.g. Ampicillin & Rifampicin → Useful in treatment of Cholecystitis & Typhoid carrier.

4- *Large Intestine*: Either via the bile or unabsorbed oral drugs.

D) Skin Glands:

1- *Sweat* → Vit B-1, Hg, As & Rifampicin → Red discoloration of sweat.
2- *Milk* → May affect suckling baby e.g. Morphine, nicotine, Purgatives, Tetracyclines & Chloramphenicol.

* Some Pharmacokinetic Parameters:

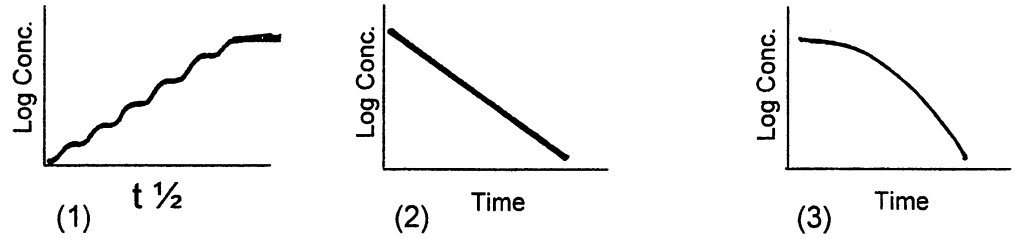
A) Plasma Half Life (t ½):

1- Time needed by the body to decrease a certain plasma concentration of a drug to its half.
2- It depends on kinetics of drug clearance from plasma (Distribution, Metabolism & Excretion).
3- For some drugs, their Biological t ½ > Plasma t ½ e.g. Reserpine → Irreversible ↓ of vesicular enzymes (Hit & Run) → Its effect does not depend on its presence in plasma. Its effect ends by resynthesis of new vesicles.
4- Repeated administration of a drug at regular intervals will reach a plateau plasma concentration (Steady State Concentration "C_{ss}") within 4-5 t1/2 (Fig 1).
5- Most of the drug (> 95%) will disappear from the body within 4-5 t1/2 after stopping its intake:

$$100\% \xrightarrow{t_{1/2}} 50\% \xrightarrow{t_{1/2}} 25\% \xrightarrow{t_{1/2}} 12.5\% \xrightarrow{t_{1/2}} 6.25\% \xrightarrow{t_{1/2}} 3.125\%$$

(↓ 50%) (↓ 75%) (↓ 87.5%) (↓ 93.75%) (↓ 96.875%)

6- t ½ is useful to determine the frequency of drug administration.



B) First-Order (Linear) Kinetics:

1- Kinetics of drug (ADME) are PROPORTIONAL to its concentration.
2- Fixed FRACTION/TIME is eliminated → LINEAR drug disappearance curve (Fig. 2).
3- CONSTANT t1/2.
4- AUC is PROPORTIONAL to drug concentration.
3- *Examples* : SD of Aspirin, Phenytoin & Alcohol.

C) Zero-Order (Saturation) Kinetics:

1- Limited capacity of drug's kinetics due to SATURATION of involved enzyme &/or carrier.
2- Fixed AMOUNT/TIME is eliminated → NON-LINEAR drug disappearance curve (Fig. 3).
3- t1/2 increases with drug conc.
4- AUC is NOT proportional to drug concentration.
3- If rate of intake of drug > Rate of its elimination → Cumulation → ↑ C_{ss} → Toxicity.
4- *Examples* : LD of Aspirin, Phenytoin & Alcohol.

	First-Order (Linear) Kinetics	Zero-Order (Saturation) Kinetics
1- Rate of Kinetics :	Directly ∝ Concentration	Saturated (Fixed) NOT ∝ Conc.
2- Elimination :	Fixed Fraction/Time	Fixed Amount/Time
3- Drug disappearance Curve:	Linear	Non-Linear
4- Half life (t1/2) :	Constant	↑ with concentration.
5- Area Under Curve (AUC):	∝ Concentration	Not ∝ Conc. → ↑C_{ss} → Toxicity.
6- Examples :	SD Aspirin, Phenytoin & Alcohol	LD Aspirin, Phenytoin & Alcohol

* *Methods Used To Prolong Duration Of Action Of Drugs:*

1- Delay Absorption:

a- Add Vasoconstrictor e.g. Adrenaline to Local anesthetics.
b- Add Oil to Vasopressin
c- Add Gelatin to Heparin.
d- Use Sparingly soluble preparation e.g. Protamine Zinc Insulin *Suspension.*
e- Use S.C. pellet implantation e.g. DOCA in Addison's disease & Contraception.
f- Use Sustained release or Controlled release or Multiple release preparation → Long duration → Less frequent administration → Improve patient compliance

2- Decrease Metabolism: Use enzyme inhibitors e.g. cimetidine & grapefruit.

3- Decrease Excretion: Probenecid → ↓ Renal excretion of Penicillin

4- Increase Binding to Plasma Proteins: Long acting sulfonamides

* *Evaluation of a New Drug in Comparison with a Standard Drug or a Placebo:*

1- Open Trial: The investigator and the patient know which of which.
2- Single Blind Trial: Only the investigator knows but not the patient.
3- Double Blind Trial: Neither the investigator nor the patient know which of which. Less bias → Best clinical results.

Dosage Forms (الشكل الصيدلي للدواء)

According to the *ROUTE* of administration *(See page 17)*:

Enteral	Others
1- Buccal e.g. Sublingual 2- Oral 3- Rectal	1- Parenteral e.g. Injection 2- Inhalation 3- Topical

I- Buccal Dosage Forms:

Drugs are put in the mouth and they are *NOT* swallowed → Either local or systemic effects.

1- Sublingual pellet *(See page 18)* → Systemic effect.
2- Buccal Spray: Spray under the tongue → Systemic effect e.g. Nitroglycerine
3- Lozenge (قرص استحلاب): Tablet, usually big, to be dissolved slowly in mouth.
4- Mouth paint (مس للفم): Usually contains antiseptic and local analgesic.
5- Mouth wash and gargle (مضمضة وغرغرة)

II- Oral Dosage Forms *(See page 17)*:

- Drugs are taken via the mouth and swallowed → Either Local or Systemic effects.
- Either Solid forms or Liquid forms

A) Solid Oral Dosage Forms:

1- Powder: Contained in a bottle or packet e.g. Oral Rehydration.

2- Effervescent granules (حبيبات فوارة) in a bottle of packet: To mask bad taste of the drug and ensure its complete dissolution e.g. Aspirin.

3- Tablets (أقراص): Drugs are compressed in a discoid form
   a- *Simple*
   b- *Sugar coated*: To mask bad taste
   c- *Enteric coated*: Covered by acid resistant coat e.g. Shellac or Keratin → Dissolve in alkaline pH of intestine → Release of contents → Useful for drugs that are irritant to stomach (Sodium salicylate) or drugs destroyed by gastric acidity.
   d- *Sustained release* (SR) = *Controlled release* (CR) = *Timed release* (TR) = *Retard*: Drugs are enclosed in coats with different dissolution rates in GIT → Slow uniform release and absorption of drug → Long duration of action with less variability in plasma concentration → Less frequent intake of drug → Better patient compliance.

4- Capsules: Drugs are put in gelatin containers either soft (for liquids) or hard (for powder and granules).
   a- *Hard gelatin* capsule containing either powder or granules.
   b- *Enteric coated* capsule.
   c- *Sustained Release* Capsule.
   d- *Soft capsule* containing liquid e.g. Oil.

B) Liquid Oral Dosage Forms: Either in Aqueous vehicle or Alcoholic vehicle.

1- Aqueous Preparations:
   a- *Decoction* (مغلي): Raw material e.g. plant leaves are boiled in water.
   b- *Infusion* (منقوع): Soak raw material in cold or hot water.
   c- *Solution* (محلول): Drugs are completely dissolved in water.
   d- *Mucilage*: Gum in water, useful as suspending and emulsifying agent.
   e- *Suspension* (معلق): Insoluble powder suspended in water by the use of emulsifying agent e.g. gum. Shake well be fore use.
   f- *Emulsion* (مستحلب): Fixed oil dispersed in water by the use of emulsifying agent e.g. gum. Shake well before use.
   g- *Aromatic water*: Volatile oil in water.
   h- *Mixture* (مزيج): More than one active ingredient in the preparation.
   i- *Syrup* (شراب): Sweetened, flavored and colored preparation.

2- Alcoholic Preparations:
   a- *Tincture* (صبغة): Extraction of active ingredient in alcohol.
   b- *Spirit* (روح): Volatile oil in alcohol.
   c- *Elixir* (إكسير): Sweetened, flavored and colored hydroalcoholic preparation that contains 25% alcohol.

III- Rectal Dosage Forms *(See page 19)*:

1- Solid = *Suppository* (لبوس شرجي).

2- Liquid = *Enema* (حقنة شرجية) either Evacuant or Retention.

IV- Parenteral Dosage Forms *(See page 19)*:

A) *Subcutaneous Pellet Implantation*.

B) *Injection*: In the form of solution, suspension, oil or powder for reconstruction. May be contained in

1- *Ampoule* (أمبول) : For single use.

2- *Vial*: Small bottle for either single or multiple use.

3- *Bottle*: Big container for IV solutions.

V- Inhalation Dosage Forms *(See page20)*:

1- Gas in cylinders: Oxygen, carbogen & Nitrous oxide.

2- Volatile liquid: Halothane.

3- Solution aerosol: Spray, atomizer or Nebulizer e.g. Salbutamol.

4- Finely micronized powder: Spinhaler e.g. Cromoglycate.

VI- Topical Dosage Forms:

A) Skin:

1-*Ointment* (مرهم): Fatty base immiscible with water for dry lesions.

2- *Cream* (كريم): The base is miscible with water, suitable for oozing lesions.

3- *Lotion* (غسول): Aqueous base applied withOUT rubbing.

4- *Liniment* (مروخ): Applied on skin with rough rubbing e.g. camphor as counter-irritant.

5- *Dusting powder*: Either protective e.g. talcum powder or medicated.

6- *Paint*: e.g. Tincture iodine

7- *Spray*.

8- *Collodion*: Nitrated cellulose + Colophony resin dissolved in Ether + Alcohol → Apply to skin → Ether and Alcohol evaporate leaving thin flexible layer.

9- *Transdermal Delivery System (TDS)*: Aiming for absorption of drug from the skin to produce systemic effect:
   a- Transdermal patch: Nitroglycerine, nicotine, hyoscine & clonidine.
   b- Cream and Ointment: Nitroglycerine.
   c- Iontophoresis: by the use of galvanic electric current e.g. Methacholine.

B) Eye: Drops, ointment, lotion & Oculosert (thin film containing the drug put in conjunctival sac).

C) Ear: Drops and ointment.

D) Nose: Drops, spray & inhalers.

E) *Vagina*: Tablet (simple or foaming), Ovule (pessary = suppository), douche & cream.

Sources of Drugs

A) Synthetic:

1- Chemical: Aspirin, Barbiturates & Sulfonamides.
2- Bio-synthetic (Bio-technology): Recombinant DNA → Human Insulin

B) Semi-synthetic: Heroin (Di-Acetyl-Morphine) & Methyl-ergometrine

C) Natural:

1- Minerals: $MgSO_4$, Iron, Iodine & Radioactive isotopes ^{131}I & ^{32}P.
2- Animals: Thyroxin, Insulin, Heparin & Vit D.
3- Micro-organisms: e.g. Fungi → Antibiotics & Ergot alkaloids
4- Plant:
   a- Roots of Ipecacuanha → Emetine
   b- Bark (Stem) of Cinchona → Quinine & Quinidine
   c- Leaves of Digitalis → Digitoxin & Digoxin
      Belladonna → Atropine
   d- Fruits of Papaver somniferum → Morphine
   e- Seeds of Nux vomica → Strychnine

Nature of Drugs

1- Alkaloids:

1- Basic Nitrogenous substances.
2- Insoluble in water, but their acid salts are soluble
3- Examples: Atropine, Morphine & Strychnine.

2- Tannins:

1- Basic phenolic Non-nitrogenous substances
2- Example: Tannic acid, present in tea.
3- They can precipitate:
   a- Surface proteins → Astringent → Useful in bleeding gum.
   b- Alkaloids → Useful as stomach wash in oral Strychnine poisoning
   c- Heavy metals e.g. Iron → Tea is contraindicated in anemic patients

3- Glycoside:

1- On severe acid hydrolysis →
   a- Sugar part (Glycone) → Responsible for the Pharmacokinetics (ADME).
   b- Non-sugar part (Aglycone or Genin) → Pharmacodynamics (Actions & Toxicity)
2- Example: Digitalis (Heart) & Aminoglycosides (Antibiotics)

4- Oils:

1- **Fixed** oils: Glyceryl ester of high M.W. fatty acids e.g. Olive & Castor oils.
2- **Volatile** oils: Mainly hydrocarbons e.g. Peppermint, Menthol & Camphor
   They produce → Mild irritation, Spasmolytic, Stomach & Carminative.

5- Plant Exudates:

1- **Resins**: Polymerized oxidized volatile oils e.g. Mastic. They are usually irritant.
2- **Oleoresin**: Volatile oil + resin e.g. Turpentine.
3- **Gums**:
   a- Chemically related to polysaccharides.
   b- Used mainly as suspending & emulsifying agents.
   c- Examples: Gum Acacia (Arabica) & Gum Tragacanth.

Drug Interactions

* *General Consideration:*

1- May be of *Practical* significance or just of *Theoretical* interest.
Significant interactions occur with drugs with:
a- Hazardous adverse effects e.g. MAO-I (Anti-depressants) + Tricyclic antidepressants → Hyperpyrexia, convulsions & DEATH.
b- Critical blood level (Narrow safety margin) e.g. Theophylline & Digitalis.

2- May be:
a- *Desirable*: Caffeine + Ergotamine in Migraine headache.
b- *Undesirable*: Adrenaline + Halothane → Cardiac arrhythmias.

3- Drug interactions depend on:
a- Dose of the drug.
b- Age of the patient: Old age → ↓ Plasma protein binding, ↓ Hepatic & ↓ Renal clearance.
c- Pathological state of the patient
d- Patient's susceptibility: May be genetically determined.

4- *More* than One mechanism may be involved: Sulfa → ↓ Metabolism & Displaces oral anti-coagulants & oral hypoglycemics → Potentiation.

5- Drug interaction may result into → Addition, Synergism, Potentiation, Antagonism or Reversal.

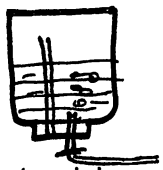
* *Mechanisms of drug Interactions;*

I- Before Administration (Outside the Body):

1- During Pharmaceutical Formulation: 

♦ Calcium lactate as filler (diluent) in Tetracycline capsules → Chelation.

2- Mixing Drugs + I.V. Infusion Fluids: 



a- May → Change pH, Solubility, or Activity of the components.
b- $CaCl_2$ → $NaHCO_3$, Tetracyclines & Cephalosporins.
c- Heparin → Hydrocortisone Na, Benzyl-penicillin, Erythromycin & Gentamicin
d- Dextran → Ampicillin, Barbiturates & Ascorbic acid (Vit C)

3- Mixing Drugs Prior (Before) Administration:

a- Protamine zinc insulin + Soluble insulin → Precipitation of Soluble insulin
b- Protamine (Base) e.g. Protamine Zinc Insulin + Heparin (Acid) → Neutralization
c- Thiopentone (Alkaline) + Succinylcholine (Acid) → Neutralization
d- Kanamycin + Methicillin → Antagonism

II- After Administration (Inside the Body):

A) Pharmacokinetics (A. D. M. E.):

1- G. I. T. Absorption:

a- Gastric Emptying:

- Metoclopramide → ↑ Gastric emptying → Enhance absorption of Paracetamol & Propranolol but decrease absorption of Digoxin
- Atropine & Propantheline → ↓ Gastric emptying → The Reverse.

b- pH Changes:

- Gastric acidity → ↑ Absorption of weak acid drugs eg Aspirin & Phenobarbitone
- Intestinal Alkalinity → ↑ Absorption of weak base drugs e.g. Ephedrine

c- Binding & Chelation:

- Ca, Mg, Al & Iron → Chelation of Tetracyclines
- Cholestyramine & Activated Charcoal → ↓ Absorption of many drugs.

d- Epithelial Structure of Gut Wall:

- Phenytoin → ↓ Absorption of Folic acid
- Para-amino-salicylic acid (PASA) & Colchicine → ↓ Absorption of Vit B-12
- Neomycin → ↓ Absorption of digitalis & Penicillins.

2- Plasma Protein Binding:

Aspirin, Phenylbutazone, Clofibrate & Sulfa → Displace:

a- Oral Anti-coagulants (Dicumarol) → Bleeding
b- Oral Hypoglycemics (Tolbutamide) → Hypoglycemia
c- Bilirubin in Neonate → Jaundice & Kernictrus.

3- Biotransformation:

a- HME Inducers: Phenytoin, Phenobarbitone, Rifampicin, Testosterone & Tobacco smoking → ↑ Their own metabolism & Other drugs.
b- HME Inhibitors: MAO-I, Cimetidine, Estrogen, Na Valproate & Chloramphenicol.

4- Renal Excretion:

a- Competition for Active Tubular Excretion:
- Probenecid → ↓ Excretion of penicillin → Prolongs its duration of action
- Probenecid → ↓ Excretion of Frusemide → Antagonize its diuretic effect
- Quinidine → ↓ Excretion of Digoxin→ ↑ Its plasma concentration

b- pH Changes:
- Acidification of urine (NH_4Cl) → ↑ Excretion of Weak base drugs e.g. Ephedrine
- Alkalinization of urine ($NaHCO_3$) → ↑ Excretion of weak acid drugs e.g. Aspirin

B) Pharmacodynamic Interactions:

1- Receptor Sites:

a- A.Ch. & Atropine on Muscarinic receptors
b- Adrenaline & Propranolol on β-Adrenoceptors
c- Morphine & Naloxone on Opiate receptors

2- Nerve Terminal:

a- Guanethidine → ↓ Neuronal uptake-1 of Noradrenaline → Supersensitivity.
b- Tricyclic Antidepressants → ↓ Neuronal uptake-1 of Guanethidine → Antagonize its Anti-hypertensive effect.

3- Physiological System:

a- Ethanol & Chlorpromazine → ↑ Other CNS Depressants.
b- Caffeine → Antagonizes CNS Depressants.
c- Ether & Streptomycin → ↑ Curare-induced Sk.m. paralysis.
d- Adrenaline → Antagonizes Histamine-induced bronchospasm.

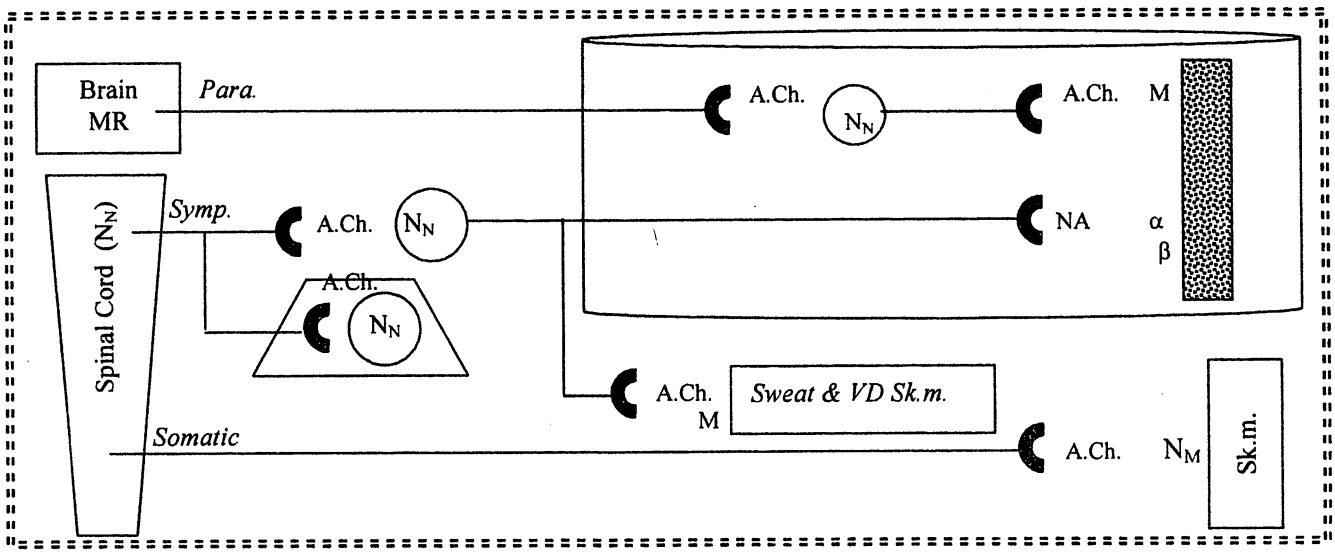
4- Blood Volume and / or Electrolytes:

a- Thiazide & Loop diuretics → Hypokalemia → ↑ Digitalis toxicity.
b- Phenylbutazone & Mineralocorticoids → Fluid retention → Antagonize Diuretics

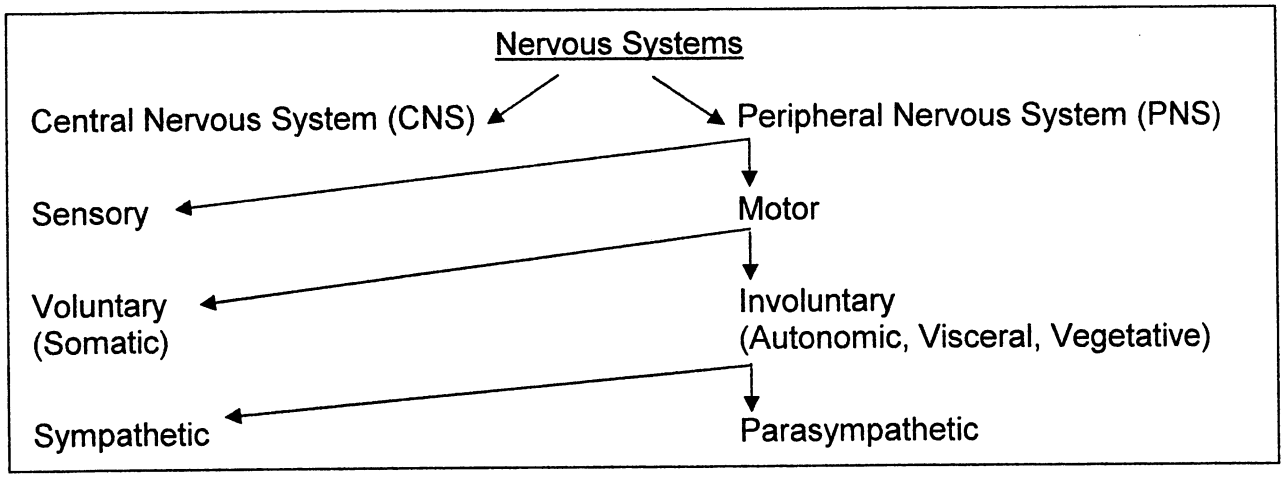
5- ILL-Defined Mechanisms:

a- Frusemide → ↑ Nephro-toxicity of Cephalosporins
b- Methoxyflurane + Tetracyclines → ↑ Risk of Renal Failure

Autonomic Nervous System



Autonomic Nervous System (A.N.S.)

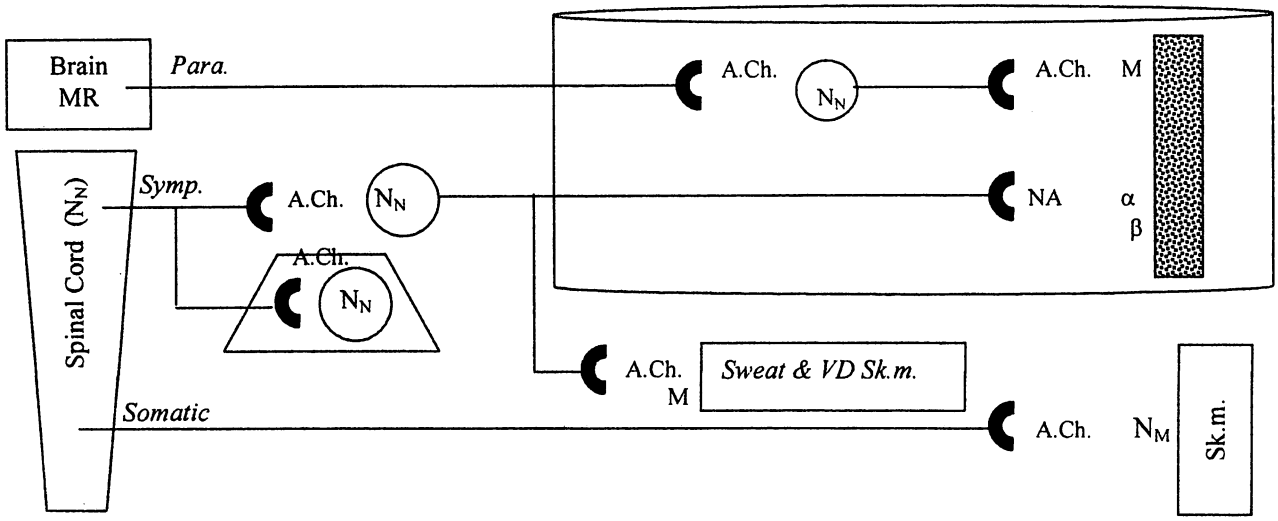


	Somatic	Autonomic
1- Actions	Voluntary	Involuntary
2- Supply	Skeletal muscles	Cardiac & smooth muscle, and Exocrine glands
3- Relay	***NO*** Ganglia	Ganglia
4- Innervations	Single innervation	***Dual*** (Double) Innervation (Symp. + Para.)

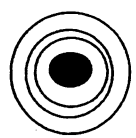
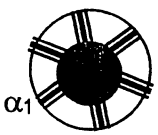
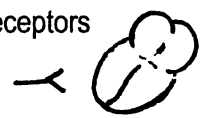
* Central Control of A.N.S.:

1- ***Hypothalamus***:
   a- Anterior part → Trophotropic → Parasympathetic.
   b- Posterior part → Ergotropic → Sympathetic
2- ***Medulla Oblongata***:
   a- Vagal center (Cardio-Inhibitory Center, CIC) → Parasympathetic
   b- Vaso-Motor-Center (V.M.C.) → Sympathetic
3- Midbrain & Spinal cord.
4- Cerebral cortex & Limbic system → Psychic & emotional effects on A.N.S.

* Types of Autonomic Nerves → Sympathetic & Parasympathetic



Autonomic Nervous System

	Parasympathetic	Sympathetic
A) Anatomy:		
1- Origin:	Cranio-Sacral Cranial nerves III, VII, IX & X Sacral segments 2,3 & 4	Spinal Thoraco-Lumbar From 1st Thoracic → 3rd Lumbar
2- Ganglia	Usually terminal or embedded in supplied organ	Usually para- & peri-vertebral in the sympathetic Chain
	Isolated Organs contain ONLY Parasympathetic Ganglia	
3- Pre-ganglionic	Long	Short
4- Post-ganglionic	Short	Long
	Most of organs receive Dual Innervation EXCEPT	
5- Innervation	Constrictor Pupillae Muscle (CPM) ***ONLY*** Parasympathetic → A.Ch. ***ONLY*** Muscarinic receptors *Para.* ——< *A.Ch.* → *M.R.* 	1- Dilator Pupillae Muscle (DPM) ——< N.A. α_1  ***ONLY*** Symp. → Noradrenaline → α-receptors 2- Ventricles of the heart  3- Most of small blood vessels ***ONLY*** Symp. → N.A. → α-receptors ——< NA → > α ***BUT*** they contain non-innervated M.R. # MR  4- Adrenal medulla = Symp. Ganglia 5- Sweat glands:  a- Thermoregulatory → Cholinergic → A.Ch → M.R. b- Apocrine → Adrenergic → N.A. → α-receptors 6- Pilomotor (Erectoepillae) muscle. 
B) Physiology:		
1- Chemical Transmitters:		
a- Ganglia	*Acetylcholine (A.Ch.)*	A.Ch.
b- Post-ganglionic	*A.Ch*	Noradrenaline (NA) = Adrenergic ***EXCEPT*** thermoregulatory sweat glands and V.D. fibers to skeletal muscle → A.Ch. = Cholinergic
2- Control	*Most of Organs* Except Blood vessels & sweat glands	Blood vessels & Sweat glands

	Parasympathetic	Sympathetic
3- Actions:	*Usually Antagonistic But Both ↑ Atrial Conductivity & ↑Salivation*	
a- Type	Usually Localized	Usually Generalized
b- Aim:	Conserve energy & Discharge excreta	Stress (Fight & Fright)
c- Pupil:	Constricted → Miosis	Dilated → Mydriasis
d- Salivation:	↑ Profuse Watery	↑ Viscid
e- Bronchi:	Constricted	Broncho-dilatation
f- Heart:	↓ All properties *BUT* ↑ Atrial conductivity ↓ Cardiac Output (C.O.P.)	↑ All properties ↑ C.O.P.
g- Bl.p.:	↓ Hypotension	↑ Hypertension
h- G.I.T.:	↑ Wall & ↓ Sphincters → Defecation	↓ Wall & ↑ Sphincters
i- U.B.:	↑ Wall & ↓ Sphincters → Urination	↓ Wall & ↑ Sphincters
j- Sex organs:	Erection	Ejaculation

* *Chemical Transmitters:*

Chemical substances released from stimulated nerve ending (terminal or varicosity) in response to nerve action potential → Bind with specific receptors on effector organs.

A ***receptor*** is a chemo-sensitive macromolecule that combine selectively with a ***ligand*** (Chemical transmitter or hormone or drug) → Complex → Effect (response).

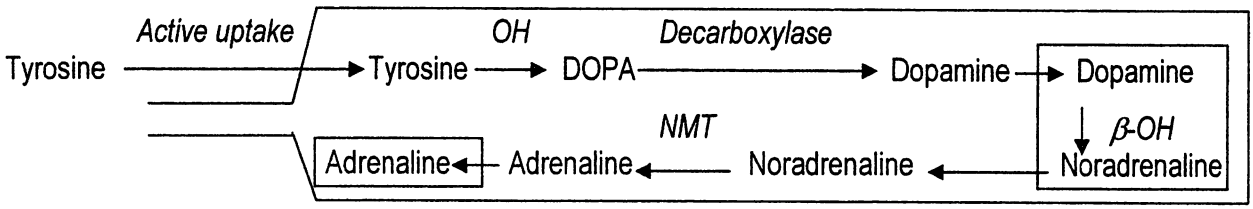
Nerve fibers and receptors are named after the chemical transmitters:

1- A.Ch. → Cholinergic nerve & Cholinergic receptor = Cholinoceptor.
2- Noradrenaline (N.A.) → Adrenergic nerve & Adrenergic receptor = Adrenoceptor.
3- Other transmitters e.g. A.T.P. → Non-Adrenergic Non-Cholinergic (NANC) → They act as co-transmitters or neuro-modulators.

Sympathetic Nervous System

* Adrenergic Transmission:

1- Synthesis:



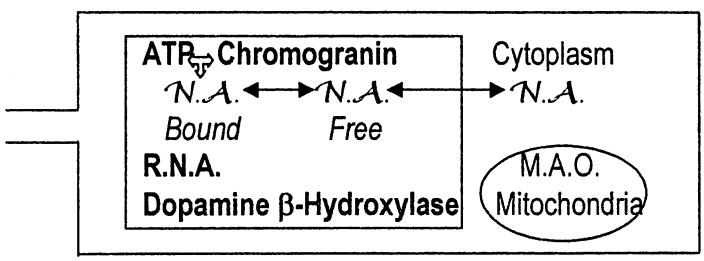
a- *Tyrosine hydroxylase*:
- Cytoplasmic *Step-Limiting* enzyme → Synthesis of DOPA
- Inhibited by cytoplasmic N.A. (-ve feed back) & Metyrosine.

b- *DOPA Decarboxylase* (L-Aromatic Acid Decarboxylase):
- Cytoplasmic enzyme → Synthesis of Dopamine & Serotonin
- Inhibited by α-Methyl DOPA *(Aldomet)*, Carbidopa & Benserazide.

c- *Dopamine β-Hydroxylase* → The ONLY Vesicular (Granular) enzyme.

d- *Phenyl-Ethanolamine N-Methyl Transferase (N.M.T.)*:
- Cytoplasmic enzyme present in A-cells of adrenal medulla & some CNS neurons → Converts Noradrenaline to Adrenaline → Store in granules.
- Stimulated (induced) by Cortisol.

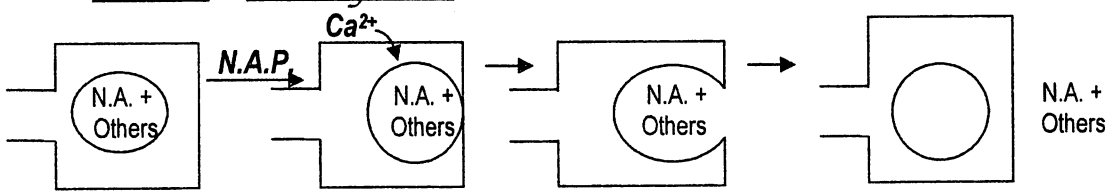
2- Storage:



* Any drug ***BOUND*** to protein:
1- NOT pass
2- NOT active
3- NOT metabolized
4- NOT excreted
5- Store = Depot form

a- In specific membrane bound vesicles (granules) to protect from M.A.O.
b- N.A. is bound to ATP (4:1) & Chromogranin (protein). Some N.A. is free.
c- There is also R.N.A. & Dopamine β-Hydroxylase enzyme.

3- Release = *Exocytosis*:

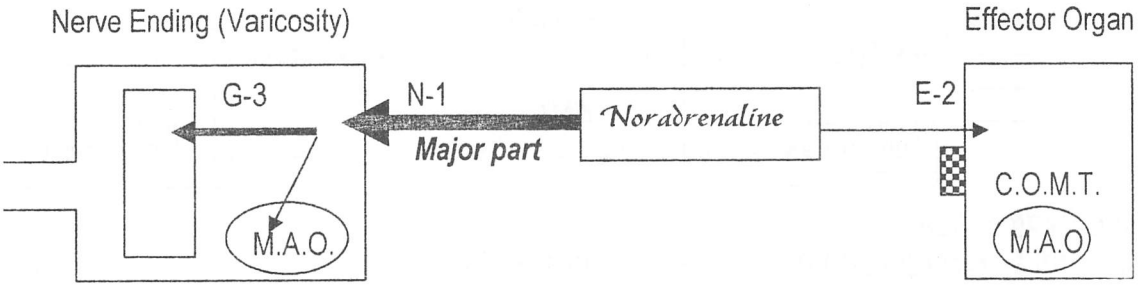


a- Arrival NAP → Depolarization → Influx of Ca^{2+} (***NB*** Mg^{2+} inhibits exocytosis) → Fusion → Lysis → Release of vesicular contents (N.A. + Others) = *EXOCYTOSIS*.
NB) *Burn & Rand Theory*: Adrenergic neurons release at first A.Ch. that facilitates subsequent release of N.A.

4- Effect = Response:

a- Noradrenaline reacts with specific adrenoceptors (α + β).
b- Change activity of effector organ e.g. ↑ Heart & ↓ Wall of intestine.

5- Fate:

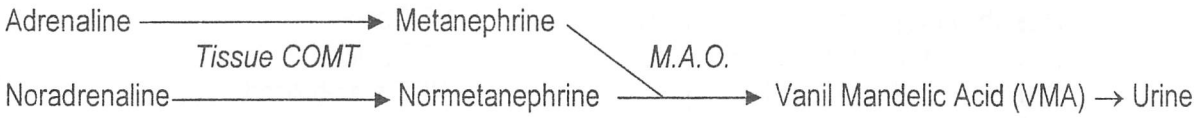


a- Reuptake:

- The ***MAJOR*** part of endogenously released N.A. undergoes ***Neuronal uptake -1*** → Some NA is inactivated by mitochondrial MAO → Then the ***MAJOR*** part undergoes ***Granular (Vesicular) Uptake-3*** → Protected from M.A.O.
- Few N.A. undergoes ***Extra-neuronal uptake-2*** by effector organs → Metabolism by Cytoplasmic C.O.M.T. & Mitochondrial M..A.O.

b- Metabolism by Specific Enzymes:

- *Mono-Amine Oxidase (M.A.O.)*: Mitochondrial enzyme presents in nervous & non-nerves tissues → Oxidative deamination. Two types A & B. Specific MAO Inhibitors.
- *Catechol-O-Methyl Transferase (C.O.M.T.)*: Cytoplasmic enzyme mainly in tissues.



N.B.)

1- ***Vanil Mandelic Acid*** (V.M.A., 3-Methoxy 4-Hydroxy Mandelic acid) → Urine. 24 hours urine contains 2-6.5 mg VMA & some adrenaline, NA, Metanephrine & Normetanephrine. IF VMA > 26 mg/day → ***Pheochromocytoma***.

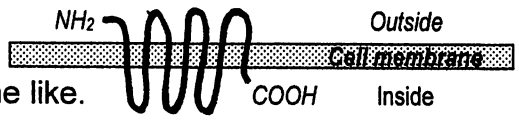
2- ***↓ Neuronal Uptake-1*** e.g. Cocaine → ↑ N.A. in synapse → ↑ Sympathetic activity.

3- ***↓ Granular uptake-3*** e.g. Reserpine → ↑ N.A. in cytoplasm → Metabolism by MAO → Depletion of Granular N.A. → ↓ Sympathetic activity.

4- ***Any factor ↓ fate of N.A.*** e.g. sympathectomy, ganglion blockers, adrenergic neuron blockers, MAO.I. & Thyrotoxicosis → ↑ Response to N.A. → ***Supersensitivity***.

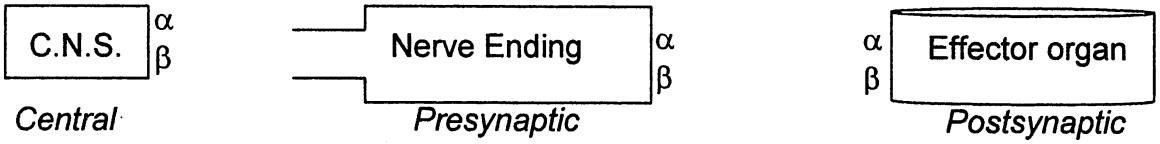
Adrenergic Receptors (Adrenoceptors)

Membrane bound receptors linked to G-protein.
They traverse cell membrane 7 times → Serpentine like.



* Types:

1- Types Alpha (α) & Beta (β). Subtypes α_1, α_2, β_1, β_2 & β_3.
2- In C.N.S. (Central), on Nerve ending (Presynaptic) & on effector organ (Postsynaptic)



I- Alpha-1 Receptors:

1- Sites: Mainly Post-synaptic on effector organs.

2- Mechanism: ↑ α_1 + G-protein → ↑ Phospholipase C (PLC) → Metabolism of membrane Phosphatidyl Inositol → Inositol triphosphate (IP_3) & Di-Acyl Glycerol (DAG) → ↑ Intracellular Ca^{2+} + Calmodulin → Cellular effects → Response.

3- Actions: (فـزع و فـرار)
a- Contraction of pilomotor muscle → erection of hair.
b- ↑ Contraction of dilator pupillae muscle → Active Mydriasis.
c- Generalized V.C. specially skin, m.m. & renal.
→ ↑ Total Peripheral Resistance (TPR) → Hypertension.
d- ↑ Viscid salivation.
e- Spasm of G.I.T. & U.B. sphincters.
f- Ejaculation & contraction of prostatic capsule.
g- Contraction of pregnant uterus.
h- Facilitate Neuro-Muscular transmission.

4- Specific Agonists e.g. *Phenylephrine.*

5- Specific Antagonist e.g. *Prazosin.*

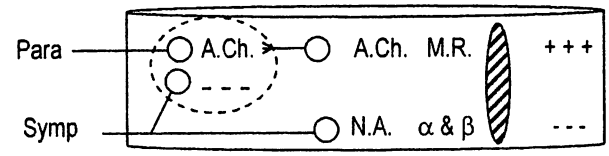
II- Alpha-2 Receptors:

1- Sites: Central (CNS), Presynaptic (Nerve ending) & Postsynaptic (Effector organ).

2- Mechanism: ↑ α_2 + G_i-protein → ↓ Adenylate cyclase enzyme → ↓ cAMP.

3- Actions: يروق الأعصاب والضغط والدم. C.N.S N.E

a- ↓ C.N.S. → Sedation & ↓ Sympathetic centers
b- Presynaptic (Autoreceptors):
- ↓ Release of N.A.
- ↓ Release of A.Ch. in enteric ganglia → Relax wall of G.I.T.
c- Kidney → ↓ Release of Renin.
d- Pancrease → ↓ Release of Insulin.
e- Fate cells → ↓ Lipolysis → ↓ F.F.A.
f- ↑ Platelet aggregation.



4- Selective Agonists e.g. *Clonidine & α-Methyl N.A.*

5- Selective Antagonist e.g. *Yohimbine.*

Beta (β) Adrenoceptors

1- Subtypes β_1,β_2 & β_3. Central, Presynaptic & Postsynaptic.
2- All βreceptors are linked to G_s-protein → ↑ Adenylate cyclase enzyme → ↑ cAMP.

I- Presynaptic β → ↑ Release of Noradrenaline.

II- Postsynaptic β_1-Adrenoceptors:

1- Mechanism: ↑ β_1 + G_s → ↑ Adenylate cyclase → ↑ cAMP →
Heart → ↑ Ca^{2+} influx & release from sarcoplasmic reticulum → ↑ Heart.

2- Actions: ينبه مراكز القيادة ويعكر الدم
a- ↑ C.N.S. → Anxiety
b- ↑ Heart → ↑ C.O.P.
c- Kidney → ↑ rennin
d- ↑ Lipolysis → ↑ F.F.A.

CNS

3- Selective agonists e.g. *Dobutamine.*

4- Selective antagonists e.g. *Atenolol*

III- Postsynaptic β_3:

1- Mechanism: ↑ β_1 + G_s → ↑ Adenylate cyclase → ↑ cAMP.

2- Actions: ↑ Lipolysis & ↑ Thermogenesis. (يخسس)

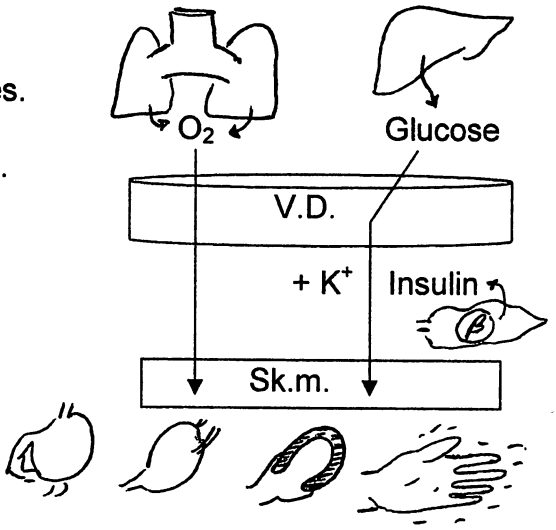
3- Selective Agonist → *Octopamine.*

IV- Postsynaptic β_2:

1- Mechanism: ↑ β_2 + G_s → ↑ Adenylate cyclase → ↑ cAMP →
In smooth muscle e.g. Bronchi → ↓ Ca^{2+} → Relaxation.

2- Actions: (تغذيـــة تامـــة للعضـــلات)

a- Generalized V.D. specially skeletal muscles.
b- Broncho-dilatation.
c- ↑ Glycogenolysis in liver & skeletal muscle.
d- ↑ Release of insulin.
e- ↑ K^+ uptake by skeletal muscle.
f- Relax G.I.T., U.B. & uterus.
g- Skeletal muscle twitches.



3- Selective agonist e.g. *Salbutamol.*

4- Selective antagonist e.g. *Butoxamine.*

Adrenoceptors

Membrane bound receptors linked to G-protein

Receptor	Mechanism	Actions	Agonist	Antagonist
α-1	G-protein → ↑ PLC → ↑ IP_3 & DAG → ↑ Ca^{2+}	- Generalized V.C. - Active mydriasis	Phenylephrine	Prazosin
α-2	G_i-protein → ↓ Adenylate cyclase → ↓ cAMP	- ↓ CNS & Symp. - ↓ Renin - ↓ N.A. - ↓ Lipolysis	Clonidine	Yohimbine
β-1	G_s-protein → ↑ Adenylate cyclase → ↑ cAMP in Heart → ↑ Ca → Stimulation	- ↑ CNS - ↑ Heart - ↑ Renin - ↑ Lipolysis	Dobutamine	Atenolol
β-2	G_s-protein → ↑ Adenylate cyclase → ↑ cAMP in smooth muscle → ↓ Ca → Relaxation	- V.D. - Bronchodilatation -Relax smooth muscle -Sk.m. twitches	Salbutamol	Butoxamine
β-3	G_s-protein → ↑ A.C. → ↑ cAMP	Lipolysis & Thermogenesis	Octopamine	

NB)

1- α + β → Relax wall of G.I.T.
2- α-1 → V.C. + Contract pregnant uterus ***while*** β-2 → The opposite
3- α-2 → ↓ Lipolysis ***while*** β-1 + β-3 → ↑ Lipolysis
4- α-2 → ↓ Renin ***while*** β-1 → ↑ Renin
5- α-2 → ↓ Insulin ***while*** β-2 → ↑ Insulin

NB) The following scheme is used in discussion of a drug or group of drugs

Name of the Drug or Group of Drugs

1- ***Definition***

2- ***Classification***

3- ***Pharmacokinetics*** = What the BODY does to the DRUG = A. D. M. E.
   a- Absorption: Oral and/or Other
   b- Distribution: Binding to plasma proteins, Blood Brain Barrie & Placental barrier.
   c- Metabolism: Hepatic and/or Other
   d- Excretion: Renal and/or Other e.g. Milk

4- ***Pharmacodynamics*** = What the DRUG does to the BODY
   a- Mechanism of action
   b- Pharmacological actions:
      - Desirable = Therapeutic effects = Uses
      - Undesirable = Adverse effects = Side effects and toxicity

5- ***Pharmacotherapeutics***:
   a- Therapeutic uses = Indications
   b- Dosage

6- ***Side effects and toxicity***:
   a- Manifestations
   b- Management

7- ***Contraindications***

8- ***Drug interactions***.

Adrenaline

Natural Sympathomimetic Catecholamine, Unstable → Adrenochrome, NOT Pass → NOT Orally & NOT BBB, Uptake & Metabolism by MAO & COMT → VMA

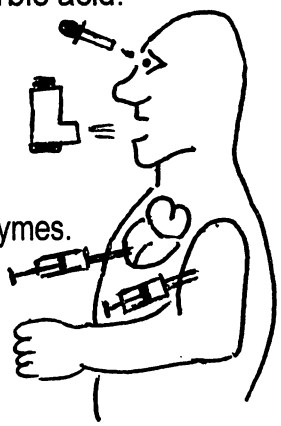
Pharmacodynamics	Pharmacotherapeutics	Adverse Effects	Contraindications & Drug Interactions
A) Local Actions:			
1-Skin → SC → α → VC	1-Add to local anesthesia	1-Gangrene of fingers	1-Around finger, toe & circumcision
2-M.M. → α → VC	2-Decongestion & haemostatic	2-Hypertension	2-Hypertension
3-Eye → α → Decongestion. ↓ IOP & NO mydriasis	3-Open angle glaucoma ***Dipivefrin* is better**	3-Cerebral hemorrhage 4-Irritate eye	3-Hemorrhagic shock
4-Inhalation → β_2 → Bronchodilatation	4-Lowei's test → Diagnose acute pancreatitis		
B) Systemic Actions:	5-Acute bronchial asthma		
1-CNS → Mild stimulation → Anxiety		5-Anxiety & headache	
2-Eye → Active mydriasis			
3-C.V.S.:			
a-Heart → β_1 → Cardiac stimulation → + ve Ino, +ve Chrono, +ve Dromo → ↑ COP, ↑ work & ↑ O_2-consumption ↑ Excitability & ↑ Automaticity	6-Cardiac resuscitation	6-Tachycardia, Palpitation, Angina & Arrhythmia	4-Tachycardia, angina & arrhythmia 5- With digitalis or General anesthesia e.g. Halothane
b-BV: Skin & mm → α → VC , Sk.m. → β_2 → VD → ↓ TPR			
c-Hypertension (↑ SBP & ↓ DBP)			6-In Supersensitivity e.g. Thyrotoxicosis
4-Bronchodilatation (β_2)			
5-G.I.T.: Relax wall (α + β) & spasm of sphincters (α)	7-Contraction ring of uterus		
6-Urinary Bladder: Relax wall (β) & spasm of sphincter (α)			
7-Uterus: Relax pregnant uterus (β_2)	8-Acute allergy		
8-Faciulitaate N-M transmission (α) & Tremors (β_2)		7-Sk.m. tremors	
9-Antiallergic: Physiological antagonist of histamine			
10- ↑ Hypothalamo-Pituitary- Adrenal → ↑ Cortisol	9-Acute hypoglycemia		
11-Metabolic:			
a-Hyperglycemia (α + β)	*Dosage Forms:		
b-Hyperlipidemia (β_1 + β_3)	1-S.C. 2-Inhalattion		
c-Hyperkalemia the (α) → Hypokalemia (β_2)	3- I.C. 4-Eye drops		

Sympathomimetics

Drugs that stimulate adrenoceptors and produce actions similar to sympathetic nerve stimulation

Adrenaline (Epinephrine)

1-Natural sympathomimetic catecholamine present in A-cells of adrenal medulla (80% of its secretion) and some neurons in CNS.
2-Unstable, if exposed to air or light → Oxidized → Adrenochrome → Red in color & very TOXIC.
Adrenaline is put in dark-glass ampoules.
3-Unstable in aqueous and alkaline media. Add acid as a preservative.
4-Stable in blood as it contains reducing agents e.g. Glutathione & Ascorbic acid.
5-The L-isomer is 20 time more potent than the D-isomer.



Pharmacokinetics:

1-Absorption:
a-NOT effective Orally → V.C. of gut mucosa & Metabolized by gut & liver enzymes.
b-Routes of Administration:
-S.C. → V.C. → Slow absorption → Long duration & less toxicity.
-Inhalation in bronchial asthma
-Eye drops in Glaucoma
-Intracardiac in cardiac resuscitation
-I.M. → V.D. → Rapid absorption → Short Duration & Toxicity (OBSOLETE)
-I.V. → Severe hypertension & Arrhythmia → Very dangerous (OBSOLETE)
2-Distribution: Catecholamines do NOT pass B.B.B.
3-Fate:
a-Major part (80%) → Metabolized by M.A.O. & C.O.M.T. → V.M.A.
b-Neuronal uptake (18%)
c-Excreted unchanged in urine (2%).

Pharmacodynamics:

Adrenaline stimulates directly ALL types & subtypes of adrenoceptors (α_1, α_2, β_1, β_2 & β_3).

A) Local Actions:

1-*Skin* → α → S.C. → V.C.
2-*Mucous membranes* e.g. Nose → α → V.C. → Decongestion & Haemostatic.
3-*Eye* → α → Decongestion & ↓ I.O.P. (↓ Synthesis of aqueous humor)
→ No mydriasis (V.C. & destruction by alkalinity of tears)
→ IF mydriasis → ***+ve Lowei's test*** = Diagnose Acute hemorrhagic pancreatitis
4-Inhalation → *Bronchi* → β_2 → Bronchodilatation
→ α → V.C. & decongestion of bronchial mucosa

B) Systemic Actions:

1-C.N.S.: Very mild stimulation → Anxiety.

2-Eye: Systemically → α_1 → ↑ D.P.M. → Active mydriasis.

3-C.V.S.:

a-Heart (Mainly β_1): ↑ ALL Cardiac properties → ↑ C.O.P.

1-+ve Inotropic (↑ Contractility)
2-+ve Chronotropic (↑ Heart rate) → Tachycardia } ***↑C.O.P.***
3-+ve Dromotropic (↑ A-V conduction)
4- ↑ Cardiac work → ↑ Oxygen needs → May cause *angina pectoris*
5- ↑ Excitability & Automaticity → May cause *arrhythmia*

b-Blood Vessels:

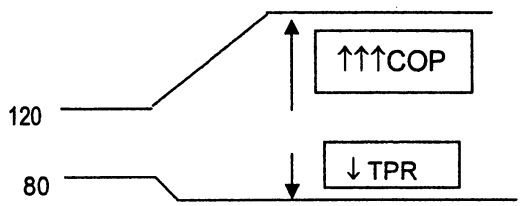
1-Skin, mucous membrane & Renal → Mainly α → VC } Minimal change in T.P.R.
2-Skeletal muscle & mesenteric → Mainly β_2 → V.D. } Therapeutic dose → ↓ TPR
3-Minimal change in TPR. Small Therapeutic dose → ***Minimal ↓ TPR*** (V.D. > V.C.)
4-Coronary V.D., due to accumulation of metabolites e.g. Adenosine.
5-Contraction of splenic capsule (α)

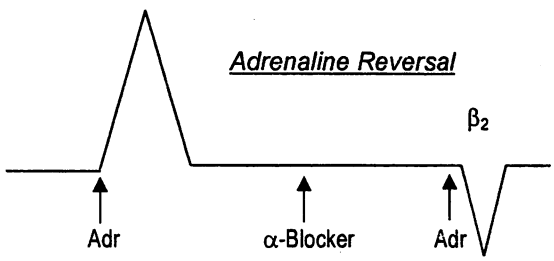
c-Blood Pressure:

$$\text{Arterial Blood Pressure} = \frac{\text{Systolic (COP) \& (T.P.R.)}}{\text{Diastolic (T.P.R.)}}$$

$$\text{Adrenaline} = \frac{\uparrow\uparrow\uparrow \text{COP} \;\&\; \downarrow \text{TPR}}{\downarrow \text{TPR}} = \frac{\uparrow \text{S} (\uparrow \text{COP})}{\downarrow \text{D} (\downarrow \text{TPR})}$$

1-Adrenaline → Marked ↑↑↑ C.O.P. & Minimal ↓ T.P.R. (V.D. > V.C.)
→ Marked ↑↑↑ Systolic & Minimal ↓ Diastolic Blood Pressures
2-**HYPERTENSION**
3- ↑ Pulse pressure
4-Hypertension of adrenaline is ***REVERSED*** by α_1 Blockers due unopposed β_2 → V.D.

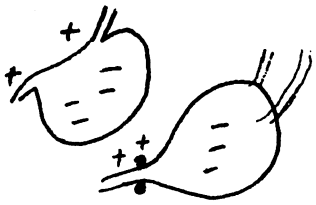




4-Respiratory System:

a-β_2 → Bronchodilatation, ↓ Mucus secretion & Improve muco-ciliary clearance
b-α → V.C. of bronchial mucosa → Decongestion
c-If sudden severe hypertension → Reflex apnea.

5-G. I. T.:



a- α → Viscid salivation & Spasm of sphincters
b- α + β → Relax wall of G.I.T.

6- Urinary Bladder:

a- α → Spasm of sphincter & Trigone
b- β → Relax wall & Detrusor muscle

7-Uterus: Variable but relaxes pregnant human uterus (B_2)

8-Skeletal Muscle:

a- β_2 → V.D., ↑ Glycogenolysis, ↑ K^+ uptake & Tremors
b- α → Facilitate N-M transmission
c-Anti-fatigue effect.

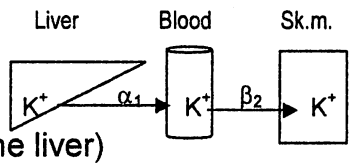
9-Anti-Allergic effect:

a-Physiological antagonist of histamine *(2 agonists, 2 receptors, 2 opposing actions)*
b-Mast cell stabilization → ↓ Release of allergotoxins e.g. histamine.

10-Endocrine: ↑ Hypothalamo-Pituitary-Adrenal axis → Release of Cortisol

11-Metabolic:

a-***Hyperglycemia***:
-Liver (β_2) → ↑ Glycogenolysis
-Pancreas (α_2) → ↓ Release of insulin
b- ↑ Skeletal muscle glycogenolysis (β_2) → ***↑Lactic acid***
c- ***↑Lipolysis*** (β_1 & β_3) → ↑ Free fatty acids
d- ***Calorigenic*** effect & ↑ Oxygen consumption
e- ***↑Blood coagulation*** due to activation of factor V
f-***Initial Hyperkalemia*** (α_1 → ↑ Release of K^+ from the liver)
→ Followed by ***Hypokalemia*** (β_2 → ↑ Uptake of K^+ by skeletal muscle)



Therapeutic Uses = Indications:

1-Added to local anesthetics (*Except cocaine*) → S.C. → α → V.C. → ↓ Absorption of local anesthesia → ↑ Duration, ↓ Systemic toxicity & ↓ Bleeding.
NB) Cocaine is a sympathomimetic (↓ Uptake-1 → ↑Noradrenaline → α → V.C.)
2-Nasal pack in epistaxis (Not in hypertension) → Haemostatic
3-Eye drops in Open Angle Glaucoma
*NB) **Dipivefrin** is better. It is a stable non-irritant prodrug → Eye → Adrenaline.*
4-Lowei's test to diagnose acute hemorrhagic pancreatitis → Mydriasis
5-Cardiac arrest → Intracardiac adrenaline → Cardiac resuscitation
6-Acute bronchial asthma (S.C. or Inhalation)
7-Contraction ring of uterus during labor (***Ritodrine*** is better → β_2 → Relax uterus)
8-Acute allergy: Angio-edema & anaphylactic shock (Adrenaline is life-saving).
9-Acute hypoglycemia

*Dosage:

1-S.C.: ½ ml of 1/1000 solution = ½ mg
2-Inhalation: 1/100 solution
3-Eye drops: 2% solution (***Dipivefrin*** is better).

*Adverse Effects of Adrenaline:

1-C.N.S.: Anxiety and headache.
2-Eye: Local adrenaline → Irritation & pigmentation (***Dipivefrin*** *is better)*
3-α → V.C. → Gangrene if injected around finger or toe, hypertension & cerebral hemorrhage. *(Prevention and treatment by α-blockers e.g. Prazosin)*
4- β_1 → Heart → Tachycardia, palpitation, angina & arrhythmia. *(Prevention & treatment by β_1-blockers e.g. Atenolol).*
5- β_2 → Skeletal muscle tremors

*Contraindications & Drug Interactions:

1-Arround finger & toes and in circumcision.
2-Hypertension
3-Hemorrhagic shock (Cause of death is renal V.C.)
4-Coronary heart disease.
5-Cardiac arrhythmia.
6-Thyrotoxicosis
7-Pulmonary embolism
8-Digitalis
9-General Anesthesia e.g. Halothane
→ Cardiac arrhythmia
10-Non-selective β-blockers e.g. Propranolol → Unopposed α → Severe Hypertension & Hyperkalemia.
11-Ganglion blockers
12-Adrenergic neuron blockers e.g. guanethidine
13-M.A.O. inhibitors
→ Supersensitivity

NB) Hemorrhagic shock:

Hemorrhage → Hypovolemia → Hypotension → Reflex V.C. → Renal V.C. → Renal failure → Death.

Noradrenaline (Norepinephrine)

(Levophed, Levarterenol)

1-Natural sympathomimetic catecholamine.
2-Chemical transmitter at ALL postganglionic sympathetic *(Except Sweat glands)*, Adrenal medulla (20% secretions), Pheochromocytoma (90%) & C.N.S.
3-Unstable (Like adrenaline) → Adrenochrome.
4-L-isomer > D-isomer

***Pharmacokinetics**:

1-NOT Orally, NOT pass BBB, Uptake & Metabolism by MAO & COMPT → VMA.
2-Administered by ***I.V. Infusion.***

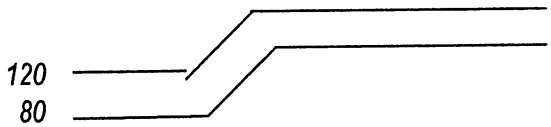
***Pharmacodynamics**:

Direct sympathomimetic MAINLY Non-selective α_1 & α_2 *and some* β_1 & β_3 ***NO*** β_2

1-CNS: Mild stimulation → Anxiety

2-Eye: Decongestion & ↓ IOP

3-CVS:



a-Blood vessels → α → Generalized V.C. *(Except coronaries)* → ↑ TPR

b-***HYPERTENSION*** elevating **BOTH S**ystolic and **D**iastolic due to ↑ **TPR**.
Minimal changed in pulse pressure.
This hypertension is **ABOLISHED** by α-Blockers.

c-Reflex ***BRADYCARDIA***: Hypertension → Reflex vagal stimulation (Mask weak β_1 effect)
Reflex bradycardia can be blocked by Atropine, ganglion blockers & α-blockers
NB) Noradrenaline on isolated heart, vagotomy or in presence of atropine, ganglion blockers or α-blockers → Tachycardia due to unmasked β_1 *effect.*
NA ↛ α → ↑ Bl.p. → Reflex Vagal → Ganglia → M-receptors → ↓ H.R.
NA → Weak β_1 ⟶ Weak ↑ H.R.(Masked by reflex ↓H.R.)

d-β_1 → +ve Inotropic → ↑ Stroke volume BUT may ↓ COP (Bradycardia)
→ ↑ Excitability & automaticity → May cause arrhythmia

COP = SV X HR

4-Respiratory: Decongestion & Reflex apnea

5-G.I.T. & Urinary Bladder: Relax wall & spasm of sphincters

6-Uterus: Contract pregnant uterus → Abortion

7-Metabolism: Hyperglycemia & Hyperlipidemia

*Therapeutic Uses:

1-Acute hypotension: Postoperative shock & during spinal anesthesia ***(I.V. Infusion*** *4 mg noradrenaline in one liter saline or glucose 5% → 1 ml/min).*
   a-Needle strictly in vein. If extravasation → gangrene
   b-Monitor Bl.p. & ECG during infusion
   c-Stop infusion gradually. If sudden stop of infusion → Severe Hypotension
2-Added to local anesthesia *(Except cocaine)*

*Adverse Effects:

1-Gangrene if injected around finger or toe
2-Hypertension → Cerebral hemorrhage
3-Bradycardia & arrhythmia
4-Abortion
5-If extra-vasation → Gangrene
6-If sudden stop → Severe hypotension

*Contraindications & Drug Interactions:

1-Around finger or toe, hypertension & hemorrhagic shock
3-Coronary heart disease, arrhythmia, digitalis & general anesthesia e.g. halothane
3-Pregnancy
4-Extravasation & Sudden stop

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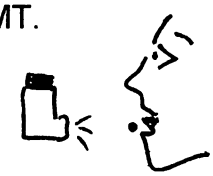
Isoprenaline
(Isopropylnoradrenaline, Isoproterenol)

Synthetic sympathomimetic *catecholamine*. NOT present in the body.

*Pharmacokinetics:

1-NOT Orally, NOT BBB, tissue uptake & Metabolism by MAO & COMT.
2-Administration:
   a-Sublingual pellet (Linguate) 10-15 mg:
      -Rapid absorption
      -Escape gut & hepatic first pass effect
      -Control of dose by spitting or swallowing excess of the dose.
   b-Inhalation 1/100 solution.



*__*Pharmacodynamics* of Isoprenaline__::

Direct Sympathomimetic *MAINLY* Non-selective β_1, β_2 & β_3 *BUT NO* α-effects

1-C.N.S.: Mild stimulation → Anxiety

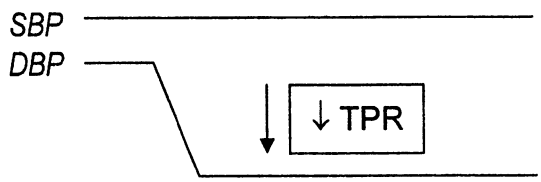
2-**C.V.S.**:

a-Heart (β_1): → +ve Ino, +ve Chrono, +ve Dromo, ↑ **COP** & ↑ Work
→ ↑ Excitability & Automaticity

b-Bl. V. (β_2) : Generalized V.D. specially Sk.m., mesenteric & Coronary → ↓ **TPR**

c-**Hypotension**:

Minimal change in SBP (↑ COP # ↓ TPR)
& ↓↓↓ **DBP** (↓ TPR) → ↑ Pulse pressure



3-Bronchodilatation (β_2)

4-Relax wall of GIT, Urinary bladder & Uterus

5-Skeletal Muscle Tremors (β_2)

6- Hyperglycemia (β_2), Hyperlipidemia (β_1 & β_3) & Hypokalemia (β_2)

***Pharmacotherapeutics**:

1-Acute Heart Block
2-Acute Bronchial Asthma

***Adverse Effects**:

1-Anxiety & headache
2-Tachycardia, Palpitation, Angina & Arrhythmia
3-Skeletal muscle tremors

***Contraindications & Drug Interactions**:

1-Coronary heart disease & Cardiac arrhythmia
2-With digitalis and general anesthesia e.g. Halothane
3-Supersensitivity e.g. Thyrotoxicosis

Dobutamine (Dobutrex)

1-*Synthetic* sympathomimetic *catecholamine* related to isoprenaline
2-**Selective β_1-agonist** → +ve Ino & +ve Dromo effects with minimal tachycardia & minimal change in TPR. Has some α-effects. ***NO*** dopaminergic effects.
3-**Used I.V. infusion** (2.5-10 ug/kg/min):
a-Cardiogenic shock & Resistant heart failure
b-Heart block

NB) ***Prenalterol***: Similar to dobutamine but Non-catecholamine → Effective Orally

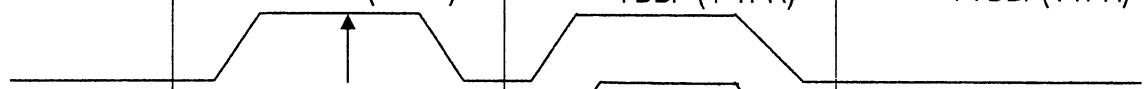
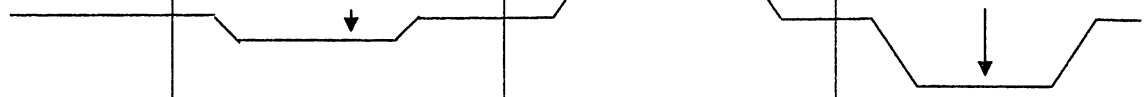
NB)

1-Arterial Blood Pressure: $\frac{\text{Systolic}\quad COP \quad \&\quad TPR}{\text{Diastolic}\qquad\qquad TPR}$

2- $\uparrow \beta_1 \rightarrow \uparrow Heart \rightarrow \uparrow COP \rightarrow \uparrow SBP$

3- $\uparrow \beta_2 \rightarrow B.V. \rightarrow V.D. \rightarrow \downarrow TPR \rightarrow \downarrow SBP \;\&\; \downarrow DBP$

4- $\uparrow \alpha_1 \rightarrow B.V. \rightarrow V.C. \rightarrow \uparrow TPR \rightarrow \uparrow SBP \;\&\; \uparrow DBP$

	Adrenaline	Noradrenaline	Isoprenaline
1-Nature	1-Natural in adrenal medulla & CNS	1-Natural in sympathetic NE, adrenal medulla, Pheochromocytoma & CNS	1-Synthetic
2-Receptors	2- α_1, α_2, β_1, β_2 & β_3	2-α_1, α_2, β_1 & β_3 **NO** β_2	2-β_1, β_2 & β_3 **NO** α
3-ABP: SBP / DBP	3-ABP: ↑SBP (↑ COP) / ↓ DBP (↓ TPR)	3-ABP: ↑SBP (↑ TPR) / ↑DBP (↑ TPR)	3-ABP: ± SBP / ↓↓DBP(↓TPR)
SBD			
DBP			
4-Pulse pressure	4-Increase	4-Minimal change	4-Increase
5-Mean Bl.P.	5- ↑ Hypertension	5- ↑ Hypertension	5- ↓ Hypotension
6-Heart rate	6- ↑ Tachycardia	6- ↓Reflex Bradycardia # by Atropine	6- ↑ Tachycardia (β_1 + ↓ Bl.p.)
7-Uses	7-See before	7-Acute Hypotension	7- Heat Block Bronchial Asthma
8-Routes	8- SC, Inhalation, Eye drops & I.C.	8- I.V. Infusion	8-Sublingual & Inhalation

Dopamine (Intropin)

1-*Natural* sympathomimetic *catecholamine*
2-*Chemical transmitter* in C.N.S. & periphery
3-Immediate *precursor* of noradrenaline

Pharmacokinetics:

1-Not Orally, Not BBB, Uptake & Metabolism by MAO & COMT → Homovanilic acid
2-Shot $t_{1/2}$ = 2 minutes. Administered by *I.V. Infusion* (2.5-10 ug/kg/min)

Pharmacodynamics:

I-Mechanism of Action:

1-Direct stimulation of specific Dopamine-receptors (D-receptors):
- a-D_1-group (D_1 & D_5 receptors) → G_s → ↑ Adenylyl cyclase → ↑ cAMP → Most of peripheral actions of dopamine e.g. Renal V.D.
- b-D_2-group (D_2, D_3 & D_4 receptors) → G_i → ↓ Adenylyl cyclase → ↓ cAMP → Most of CNS actions e.g. Anti-Parkinsonian effect
- c-Presynaptic D-receptors → ↓ Release of chemical transmitters
- d-Other D-receptor agonists e.g. Bromocriptine & Apomorphine
- e-D-receptor antagonists:
  - -Anti-psychotics e.g. Chlorpromazine & Haloperidol
  - -Anti-emetics e.g. Metoclopramide

2-Dual (Direct & Indirect through release of noradrenaline) α & β stimulation.

II-Pharmacological Actions:

A) Peripheral actions:

1-Small dose → ↑ D_1-receptors → V.D. (RENAL + mesenteric, coronary & cerebral) ↓ TPR & ↑ RBF & improve circulation of vital organs (كريم).
This action is blocked by D-blockers e.g. Haloperidol.
2-Moderate Dose → ↑ D_1 & β_1 → VD + Inotropic effect → ↑ COP with minimal tachycardia (حكيم). This action is blocked by β-blockers e.g. atenolol
3-Large dose → α_1 → V.C. → ↑ TPR (لئيم). This action is blocked by α-blockers

C) C.N.S. actions:

Dopamine does NOT pass BBB. Its precursor L-DOPA passes BBB → Dopamine by CNS dopa decarboxylase enzyme.

1-Limbic system → Euphoria & Psychosis (Schizophrenia)
2-Basal Ganglia → Anti-Parkinsonian *(Use L-DOPA)*.
3-Hypothalamus: ↑ Temperature, ↓ Appetite & ↓ Prolactin secretion
4-C.T.Z. → Nausea & vomiting

*__Therapeutic Uses of Dopamine__:

1-SHOCK (Hemorrhagic, Cardiogenic & Septic = Endotoxic):
a-Renal V.D. → ↑ R.B.F. → ↑ Urine formation.
b-Improve microcirculation of vital organs
c-Inotropic effect → ↑ COP → Maintain Bl.p.
NB)
a-Restore blood volume (Fresh blood transfusion) before using dopamine.
b-Monitor for Bl.p., E.C.G., urine output etc.
c-Decrease dose of dopamine in patients taking MAO.I.
2-Resistant heart failure

*__Adverse Effects of Dopamine__:

1-Large dose (Rapid infusion) → Tachycardia, angina, arrhythmia & hypertension.
2-Nausea and vomiting.

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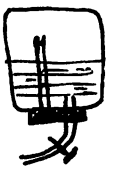
Fenoldopam (Corlopam)



1-*Synthetic* sympathomimetic *catecholamine*
2-Direct *selective* D_1-agonist → V.D. (Renal + Others) → ↓ TPR → ↓ Bl.p.
2-Used by I.V. infusion (0.025-0.05 ug/kg/min) in treatment of emergency Hypertension e.g. postoperative
3-Short $t_{1/2}$ = 5 minutes

*Remember:

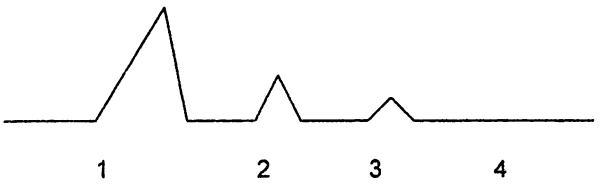
1-Heart Failure = Weak cardiac contractility → treat by +ve Inotropics
e.g. Dopamine & Dobutamine.

2-Heart Block = Slow A-V conduction → treat by +ve Dromotropics
e.g. Isoprenaline & Dobutamine

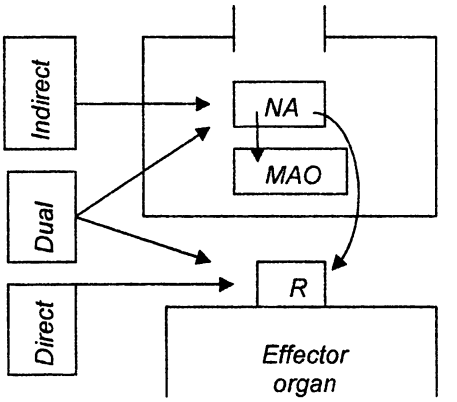
3-Shock = Severe hypotension:
a-Anaphylactic shock due to severe allergy & release of mediators e.g. histamine
Treatment by Adrenaline
b-Operative shock e.g. during spinal anesthesia → severe V.D.
Treat by Noradrenaline or other vasopressors
c-Cardiogenic shock due to myocardial infarction
Treat by Dopamine & Dobutamine
d-Hemorrhagic shock = Hemorrhage → Hypovolemia → Hypotension → Reflex V.C. → Renal V.C. → Renal failure → Death
Treat by *Fresh Blood Transfusion then* Dopamine

NB) Sympathomimetics:

	Catecholamine	Non-Catechol
1-Stability	Not Stable	Stable
2-Passage	Not Pass	Pass
3-Orally	Not Orally	Orally
4-B.B.B,	Not B.B.B.	Pass
5-Met.	Rapid	Slow or No
6-Duration	Short	Long



Tachyphylaxis = نقص استجابة حاد



	Direct	*Indirect*
1-Potency	Potent	Weaker
2-Onset of action:	Rapid	Slower
3-Sympathectomy or depletion of stores	Supersensitivity	Abolish
4-Redeated administration	Normal response	Tachyphylaxis

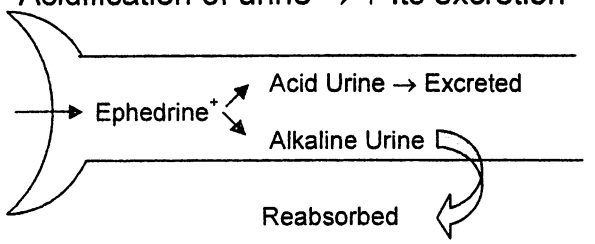
	Adrenaline	Ephedrine
1-Nature	Natural Catecholamine	Synthetic Non-Catecholamine
2-Kinetics:		
a-Absorption	Not Orally	Orally
b-Distribution	Not B.B.B.	Pass B.B.B.
c-Metabolism	Rapid by M.A.O. & C.O.M.T.	Not
d-Duration of Action	Short	Long
3-Dynamics		
a-Local on normal eye	Decongestion NO mydriasis	Decongestion + Mydriasis
b-Local on nose	Decongestion	Decongestion → Irritation → Rebound congestion
c-Sympathetic		
-Mechanism of action	***DIRECT***	***DUAL*** (Mainly "90%" INDIRECT)
-Potency	Potent	Weaker
-Onset	Rapid	Slower
-Duration	Short	Longer
-Sympathectomy or Depletion of noradrenaline stores	Supersensitivity	Decrease
-Repeated administration	Normal response	Tachyphylaxis
- α-Blockers	Reverse	Abolish
d-C.N.S. Actions	Very Weak	Potent CNS Stimulant
4-Uses:	Acute attacks	Prophylaxis
5-Adverse Effects	α + β	α + β + ↑ C.N.S.

Ephedrine^{+}

1-Sympathomimetic ***Non***-catecholamine *alkaloid*
2-Obtained from Ephedra plant or Synthetically

******Pharmacokinetics***:

1-Absorbed Orally, mucous membranes & parenterally
2-Distributed ALL over the body & passes B.B.B.
3-Not metabolized, it may ↓ M.A.O.
4-Excreted unchanged in urine
Acidification of urine → ↑ Its excretion



NB) Any Drug to Pass = Absorbed:
1-Small in size
2-Free = Non-bound
3-Lipid soluble
4-Non-ionized
5- في محيط مثله

الدواء يمتص في محيط مثله ويفرز في محيط عكسه

Drug	Absorption	Excretion
1- Acids e.g. Aspirin	Acid Stomach	Alkaline Urine
2- Bases e.g. Ephedrine	Alkaline Intestine	Acid Urine

******Mechanism Of Action***:

1-Dual (Mixed) Sympathomimetic, acts MAINLY *indirect* → Weaker, Slower, Longer & Tachyphylaxis (May be due to depletion of endogenous noradrenaline).
2-Potent C.N.S. Stimulant, but weaker than amphetamine.

******Local Actions***:

1-Skin and mucous membranes → Irritation.
2-Nose → Decongestion → Rebound congestion (Due to irritation)
3-Eye → Decongestion + ↓ IOP + Active mydriasis (Not in Negroes = Racial tolerance)

******Systemic Actions***:

1-C. N. S. Stimulation: In a descending manner

a-↑ Cerebral cortex & reticular formation (RAS) →
-Insomnia (Add hypnotic e.g. Phenobarbitone)
-L.D. → Anxiety, tremors & convulsions
-NB) Ephedrine has Sedative effect in children with *Attention-Deficit Hyperactivity Disorder* (ADHD) = Hyperkinetic syndrome in children

b-↑ Medullary centers: ↑ R.C. (Analeptic), ↑ V.M.C. & ↑ C.T.Z.

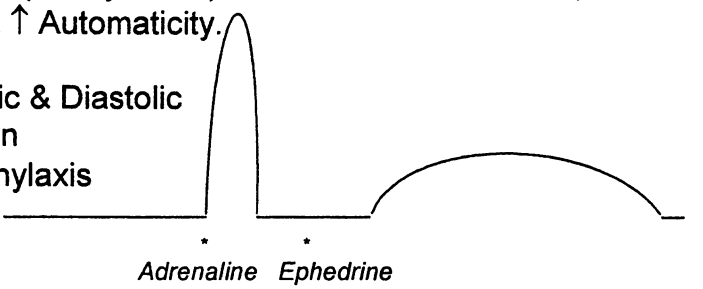
c- ↑ Spinal reflexes.

2-Eye: Active mydriasis

3-C.V.S.:

a- ↑ Heart → +ve Ino, +ve Chrono (Tachycardia), +ve Dromo → ↑ C.O.P., ↑ Work & ↑ O_2-needs. ↑ Excitability & ↑ Automaticity.

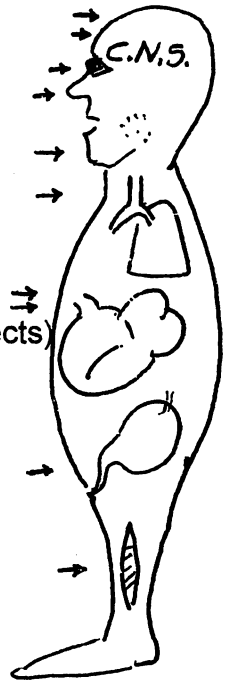
b- HYPERTENSION:
- *Moderate* rise in *BOTH* Systolic & Diastolic
- Delayed onset & Long Duration
- Repeated injection → Tachyphylaxis
- *Abolished* by α-blockers



4-Bronchodilatation
5-GIT & UB: Relax wall & spasm of sphincters
6-Uterus: Relaxes pregnant human uterus
7-Antiallergic

} Similar to Adrenaline BUT Weaker, Slower & Longer

8-Skeletal muscle stimulant: Stronger than adrenaline (CNS ↑)



*Therapeutic Uses: (25 mg Orally, S.C. & I.M.)

1-As Analeptic in toxicity with CNS ↓
2-As Sedative in children with Attention-Deficit Hyperactivity Disorder
3-Mydriatic eye drops 1-3%
4-Nasal Decongestant (*Pseudoephedrine* is better → Less adverse effects)
5-Prophylaxis of Allergy
6-Prophylaxis of bronchial asthma
7-Heart block
8-Prevent Hypotension e.g. before spinal anesthesia
9-Nocturnal enuresis
10-Myasthenia gravis (As adjuvant to Neostigmine)

*Adverse Effects:

1-CNS ↑ → Insomnia, anxiety, tremors, convulsions & vomiting (↑ CTZ).
2-CVS: Hypertension, tachycardia, palpitation, angina & arrhythmia
3-Retention of urine especially in male patients with *senile hypertrophy of prostate*
4-Tolerance & tachyphylaxis BUT NOT addiction (Unlike amphetamine)

Amphetamine+

Synthetic sympathomimetic Non-catecholamine alkaloid

Pharmacokinetics:

1-Absorbed orally, mucous membranes & parenterally
2-Distributed all over the body & passes B.B.B.
3-Metabolised slowly (Not by MAO)
4-Excretred unchanged in urine. *Acidification* of urine ↑ its excretion.

Pharmacological Actions:

- L-Amphetamine (Benzedrine) acts *mainly* as *INDIRECT* sympathomimetic
- d-Amphetamine (Dextroamphetamine, Dexedrine) acts *mainly* as *CNS Stimulant*

A) *C.N.S.*:

Powerful CNS Stimulant in a descending manner (> Ephedrine).

1-*Psychic effects*: *Due to release of central Noradrenaline & Dopamine→ ↑Cortex & RAS*
a-Small dose → Alertness, wakefulness, ↑ mental activity, delays mental fatigue, improve physical performance & *Euphoria BUT* followed by Fatigue & Depression (أسهر أذاكر طول الليل أفهم وأحفظ ومبسوط بس ثاني يوم أنام وأكتئب)
b-Moderate Dose → Anxiety, nervous tension & Tremors (أتوتر وأتخانق وأرعش)
c-Large dose → Abnormal behavior (Schizophrenia paranoid like syndrome), hyperthermia & convulsions (فصام اضطهاد جنون العظمة)
2-*Medullary centers*: ↑ R.C. (Analeptic), ↑ V.M.C. & ↑ C.T.Z.
3-↑ All *spinal reflexes*, mono & polysynaptic
4-*Analgesia*, potentiate analgesic effect of morphine
6- *Anorexigenic* → ↓ Appetite

B) ***Indirect sympathomimetic*** → Release of Noradrenaline → ↑ α mainly → Hypertension (↑ Both SBP & DBP) & reflex bradycardia (# by Atropine) → Similar to noradrenaline BUT weaker, slower, longer & Tachyphylaxis.

Therapeutic Uses:

Amphetamine produces *ADDICTION*, therefore it is *OBSOLETE*
**1-As sedative in Attention-Deficit Hyperactivity Disorders in children (No addiction)
2-Parkinsonism (It releases Dopamine in basal ganglia)
3-Chronic alcoholism
4-Psychic Depression
5-Nocturnal Enuresis
6-Fatigue physical & mental
7-Obesity
**8-Narcolepsy

*Adverse Effects of Amphetamine:

1-Long Use → ADDICTION → Physical & Psychic Dependence → Sudden stop → Withdrawal (abstinence) syndrome.
2-Insomnia, anxiety, hallucination, Schizophrenia, hyperthermia & convulsions
3-Hypertension & Anorexia

NB) Treatment of Acute Amphetamine Poisoning:

1-Acidification of urine by Ammonium chloride → ↑ Its excretion
2-Alpha blockers e.g. Phentolamine → Treat hypertension
3-Antipsychotic e.g. Chlorpromazine = Blocks D-receptors = Amphetamine Antidote
4-Anticonvulsant e.g. Diazepam

*Contraindications & Drug Interactions of Amphetamine:

1-Psychosis
2-Hypertension & coronary heart diseases
3-With MAO.I. → Severe Hypertension

NB)

1-**Methamphetamine**: More CNS ↑ & Less CVS actions than Amphetamine

2-**Tyramine**: (موجود في الجبنة القديمة والفول والزبادي)
a-Indirect sympathomimetic present in Aged cheese, Broad beans & Yogurt
b-Not effective Orally → Complete metabolism by Gut & Hepatic MAO
c-Produces severe hypertension in patients taking MAO. Inhibitors

3-**Others Anorexigenic Drugs**:

a-*Phenylpropanolamine*: Oral common cold preparations → Nasal decongestant

b-*Phenmetrazine* → ↑ CNS

c-*Mazindol* → Antidepressant

d-*Fenfluramine & Dexfenfluramine* → 5-HT mechanism → Cardiac arrhythmia

Vasopressors (α_1-Agonists)

α_1-Agonists → V.C. → ↑ TPR → ↑ Bl.p. (SBP & DBP) → Treat Hypotension

1-**Noradrenaline**: *I.V. infusion* to treat *Acute* hypotension e.g. during spinal anesthesia

2-**Ephedrine**: S.C. or Orally to *prevent* hypotension e.g. before spinal anesthesia

3-Phenylephrine (Neosynephrine):

Synthetic sympathomimetic *Non*-catecholamine

***Pharmacokinetics**:

1-Absorbed Orally, mucous membrane & parenterally.
2-Distributed All over the body
3-Metabolised, slower than Noradrenaline → Longer duration

***Pharmacodynamics**:

1-Selective, Direct stimulation of postsynaptic α_1-adrenoceptors (NO β-effects)
2-Generalized V.C. → ↑ TPR → Hypertension (↑ SBP & DBP) → Reflex bradycardia (# by Atropine. No β_1-effect → No ↑ HR after atropine).
3-Local on Eye → Decongestion, ↓ I.O.P. + Active mydriasis
4-Local on Nose → Decongestion → Irritation → Rebound congestion
5-No CNS actions
6-Other actions → See α_1-effects e.g. contraction of pregnant uterus

***Therapeutic Uses**: *Orally, locally & Parenterally*

1-Added to Local anesthetics
2-Hypotension
3-Paroxysmal Atrial Tachycardia (PAT)
4-Nasal Decongestant (Local & Oral)
5-Mydriatic & Open angle glaucoma

NB)

1-**Methoxamine & Midodrine**: Similar to phenylephrine

2-**Mephenteramine & Metaraminol**: Similar to Ephedrine → Dual mechanism

Nasal Decongestants

1-**Naphazoline** *(Privin)*:
2-**Tetrahydrozoline** *(Nazine)*
3-**Xylometazoline** *(Otrivin, Rhinex & Balkis)*
4-**Oxymetazoline** *(Iliadin, Afrin & Oxymet)*

a-Non-irritant nasal drops & sprays → No Rebound congestion
b-Non-catecholamines → Long duration
c-Long use (> 2 days) → Ischemia of nasal mucosa → Loss of smell (Anosmia) & ↑ Infection.
d-Adult concentrations in infants → Drowsiness

5-***Phenylpropanolamine*** (**Norephedrine,** *Cnota-Flu, Antiflu, Nova-C, Coldact, Flustop, Flu-Cut, Flurest, Noflu, Rhinomol, Pararhinol, Corocidin D, Rhinogesic, Contac 12 & Eskornade*):
a-Effective Orally & Topically. Used in oral common cold preparations
b-Similar to ephedrine but LESS side effects
c-↑ Both α & β-receptors → Contraindicated in Hypertension & Angina pectoris
d-Anorectic

6-**Pseudoephedrine** *(Actifed, Histarhine, Doldex-2)*: Oral common cold preparation

7-**Phenylephrine** *(Noflu, Corocidin D, Sine-up)*: Oral common cold preparations

NB) Sympathomimetics:

1-*Added to Local Anesthetics (α_1)*: **Adrenaline & Phenylephrine**

2-*Mydriatics* (α_1): **Ephedrine & Phenylephrine**

3-*Inotropics* (β_1): Adrenaline, Isoprenaline, **Dopamine, Dobutamine & Prenalterol**

4-*Vasodilators*:
a-β_2-Agonists → Useful in treatment of Peripheral Vascular Diseases (PVD) e.g. Raynod's disease
-****Isoxsuprine** *(Duvadilan, Vascular, Vasoxsuprine & Perivas)*: Oral tablets
-**Nylidrine** *(Buphenine, Arlidine)*
b-D_1-Agonist: **Fenoldopam** *(Carlopam)* I.V. infusion in emergency hypertension

5-*Uterine Relaxants (β_2)*: Treat Dysmenorrhoea, Premature labor & Contraction ring of uterus

a-Ritodrine** *(Yutopar)*: I.V. Infusion, I.M. & Oral
b-**Hexoprenaline** *(Gynipral)*
c-**Isoxsuprine**
d-**Salbutamol**
e-**Adrenaline**

6-*Anabolics (B_2)*: **Clenbuterol** → ↑ Muscle strength

7-Sympathomimetic Bronchodilators

They ↑ β_2-adrenoceptors → ↑ Adenylyl cyclase → ↑ cAMP → ↓ Ca^{2+} →
1-Bronchodilatation
2-↓ Bronchial secretion & improve muco-ciliary clearance
3-Mast cell stabilization → ↓ Its Degranulation → ↓ Release of mediators e.g. histamine

A) Non-Selective β-Agonists:

1-Stimulate $\beta_2 = \beta_1$ → Bronchodilatation = ↑ Heart rate → *Avoid in Cardiac patients*
2-Examples:

a-**Adrenaline (Epinephrine)** → ↑ $\alpha + \beta_1 + \beta_2$ → Tachycardia & hypertension

b-**Isoprenaline** → ↑ $\beta_1 + \beta_2$ → Tachycardia

c-**Ephedrine**: → ↑ $\alpha + \beta$ + CNS → Tachycardia + Hypertension + Insomnia

d-**Orciprenaline (Metaproterenol, *Alupent*)**:
-Related to isoprenaline, BUT Non-catecholamine → Not metabolized by COMT → Longer duration & effective orally
- ↑ $\beta_2 > \beta_1$ → Bronchodilatation > ↑ Heart rate.

B) Selective β_2-Agonists: *Allowed in cardiac patients*

Examples:

1-*Catcholamines*:

a-**Isoetharine** *(Bronkosol)*→ Metabolized by COMT

b-**Hexoprenaline** *(Asmadol):* Prodrug → Metabolized by COMT → Active metabolite(2).

2-*Non-Catecholamine*:

Effective Orally & Not metabolized by MAO or COMT → Long duration

a-Short Acting:

-***Salbutamol** (Ventolin)*: Orally 2-4 mg & Inhalation 100 ug/Puff

-**Terbutaline** *(Bricanyl)*: Orally 2.5 mg & Inhalation 250 ug/Puff

-**Fenoterol** *(Berotec)*: Orally2.5 mg & Inhalation 200 ug/Puff

-**Reproterol** *(Asthmabronchin)*

b-Long Acting: Useful in *PROPHYLAXIS* of bronchial asthma

-*Salmeterol (Serevent)*: 25 ug Inhalation / 12 hours

-*Formoterol (Foradil)*: 12 ug Inhalation / 12 hours

*Pharmacology of β_2-Agonists: e.g. Salbutamol

Salbutamol

♦ Synthetic Sympathomimetic Non-Catecholamine, Selective β_2-agonist

*Pharmacokinetics:

1-Absorption: Orally, mucous membranes & parenterally
2-Distributed ALL over the body
3-NOT metabolized by MAO nr COMT

*Pharmacodynamics:

1- They ↑ β_2-adrenoceptors → ↑ Adenylyl cyclase → ↑ cAMP → ↓ Ca^{2+} →
   a-Bronchodilatation
   b-↓ Bronchial secretion & improve muco-ciliary clearance
   c-Mast cell stabilization → ↓ Its Degranulation → ↓ Release of mediators e.g. histamine
2-Relax wall of G.I.T., Urinary bladder & Uterus
3-V.D. especially in Sk.m. & mesenteric vessels
4- ↑ Glycogenolysis & ↑ Release of insulin
5-Skeletal muscle twitches & ↑ uptake of K^+

*Therapeutic Uses:

1-Bronchiala asthma: Acute attacks, Status asthmaticus & Prophylaxis
2-Uterine relaxant: Dysmenorrhoea, premature labor & Contraction ring of uterus
3-Some cases of Congestive Heart Failure (↓ TPR & ↑ COP).
   (**NB**: β_2 → +ve Ino & NOT toxic to heart
   while β_1 → +ve Ino + Cardiotoxic → Cardiomyopathy & Remodeling)

*Doses:

1-Orally: 2-4 mg tds
2-Inhalation (Puff = 100 ug): 1-2 Puffs / 4-6 hours

*Adverse Effects:

1-Tremors of skeletal muscle
2-Tachycardia (Some β_1 + Reflex due to hypotension)
3-Tension and anxiety
4-Tolerance due to down-regulation of β_2-recptors
5-Hypokalemia

Classification of Sympathomimetics

A) According To *Nature*

1-**Natural** in Body: Adrenaline, Noradrenaline & Dopamine
2-**Synthetic**: the others

B) According To *Chemistry*

1-**Catecholamines** → Unstable & can NOT pass membranes
Adrenaline, Noradrenaline, Isoprenaline, Dopamine, Dobutamine, Fenoldopam, Isoetharine, Hexoprenaline & α-methyl noradrenaline (α_2-Agonist).

2-**Non-Catecholamines**: The others

C) According To *Mechanism Of Action*

1-**Direct** stimulation of adrenoceptors: Most of sympathomimetics.

2-**Indirect**:
a-Release of noradrenaline: Amphetamine & Tyramine
b-Cocaine → ↓ Neuronal uptake-1 & MAO.I → ↑ Endogenous catecholamines

3-**Dual (Mixed)**: Direct + Indirect (Release of Noradrenaline) e.g. Ephedrine

	Direct	Indirect	Dual (Mixed)
1-Example	Most of sympathomimetics	Amphetamine & Tyramine	Ephedrine
2-Sympathectomy & depletion of stores	Still active	Abolish action	Decrease action
3-Repeated administration	Normal response	Tachyphylaxis	Tachyphylaxis

D) According To *Selectivity*

1-**Alpha-Receptors**:
a-Selective α_1-agonists: Phenylephrine & Methoxamine
b-Selective α_2-agonsists: Clonidine & α-methyl noradrenaline
c-Non-Selective α_1 + α_2-agonists: Adrenaline & Noradrenaline

2-**Beta-Receptors**:
a-Selective β_1-agonist: Dobutamine
b-Selective β_2-agonist: Salbutamol
c-Non-selective β_1 + β_2-Agonists: Adrenaline & Isoprenaline

3-**Alpha + Beta Receptors**:
a-Adrenaline: $\alpha_1 + \alpha_2 + \beta_1 + \beta_2 + \beta_3$
b-Noradrenaline: $\alpha_1 + \alpha_2 + \beta_1 + \beta_3$
c-Dopamine: D + β_1 + α_1

E) According to *Main Action*

1-Vasopressors; Phenylephrine & Methoxamine

2-Nasal Decongestants: Naphazoline & Phenylpropanolamine

3-Mydriatics: Ephedrine & Phenylephrine

4-Added to Local Anesthetics: Adrenaline & Phenylephrine

5-Cardaiac Stimulants: Adrenaline, Isoprenaline, Dopamine & Dobutamine

6-Vasodilators: Nylidrine, Isoxsuprine & Fenoldopam

7- Uterine Relaxants: Ritodrine & Isoxsuprine

8-Anabolics: Clenbuterol

9-Anorexigenics: Amphetamine & Phenmetrazine

10-CNS Stimulants: Ephedrine < d-Amphetamine < Methamphetamine

Sympathetic Depressants

A) Adrenergic Receptors Blockers:

1-Alpha – Blockers: Prazosin

2-Beta – Blockers: Propranolol

3-Alpha + Beta Blockers: Labetalol

B) Adrenergic Neuron Depressants:

1- Inhibit Synthesis: Metyrosine

2-Inhibit Storage: Reserpine

3-Inhibit Release:

a-Adrenergic Neuron Blocker: Guanethidine

b-α_2-Agonsits: Clonidine

4-Chemical Sympathectomy: 6-OH-Dopamine

C) Ganglion Blockers: Hexamethonium (C-6)

D) Central Sympathetic Depressants:

1-α_2-Agonists: Clonidine

2-Inhibitors of V.M.C.: Reserpine

Alpha Adrenoceptor Blockers

*Selective α_1-Blockers:

1- Prazosin *(Minipres)*

1-Selective α_1-blocker → V.D.

2- ↓ Phosphodiesterase Enzyme: → POWERFUL V.D.
- a-↑ cAMP (= ↑ β) → ↑ Heart rate + V.D.
- b- ↑ cGMP (= ↑ M) → ↓ Heart rate + V.D.

3-Powerful Mixed V.D.:
- a-Arterial V.D. → ↓ TPR → ↓ After-load
- b-Venous V.D. → ↓ Venous return → ↓ End-diastolic volume → ↓ COP → ↓ Preload
- c- ↓ BOTH After and Pre-load

4-Hypotensive → ↓ BOTH Systolic & Diastolic blood pressures

5-Minimal change in heart rate:
- a- Tachycardia of cAMP # Bradycardia of cGMP
- b-NO α_2-block → NO ↑ release of noradrenaline

6-Relax smooth muscle of Trigone & Prostatic capsule → Easy micturation

7-***Therapeutic Uses***:
- a-Essential hypertension *better add* Diuretic + β-Blocker
- b-Congestive heart failure: ↓ Both After & Pre- load → ↑ COP
- c-Peripheral vascular diseases e.g. Raynaud's disease
- d-Pheochromocytoma *(± β-Blockers)*
- e-Senile Benign Prostatic Hyperplasia (BPH)

8-***Adverse Effects***:
- a-Initial syncopal attack = First dose phenomenon → Severe postural hypotension. Start by small dose (1mg) at bed time then increase the dose gradually.
- b-Flush and nasal congestion
- c- ↓ COP → ↓ RBF → ↓ Urine formation → Fluid retention (Add Diuretic)
- d-Failure of ejaculation
- e-Postural hypotension

*NB) Other Srelective α_1-Blockers:

1-**Doxazosin** *(Cardura)*
2-**Terazosin** *(Terazin)*
3-**Alfuzosin** *(Xatral)*

Similar to Prazosin, but Longer t1/2 → Once daily (od). Also useful in BPH.

4-**Tamsulosin** (Flomax): Selective α_{1a}-blocker. ***More*** effective in ***BPH*** & less CVS.

5-**Indoramine**:
- a-α_1-Blocker
- b-Direct myocardial depressant
- c-Local anesthetic
- d-Antihistaminic

*Non-Selective α_1 & α_2-Adrenoceptor Blockers:

A) Imidazoline Derivatives:

- **Phentolamine** *(Regitine)*
- **Tolazoline** *(Priscol)*

1-**Non**-Slective α_1 & α_2-adrenoceptor block:
  a-Block ***post***synaptic $\alpha_1 \rightarrow$ V.D.
  b-Block ***presy***naptic $\alpha_2 \rightarrow \uparrow$ Release of noradrenaline $\rightarrow \uparrow \beta_1 \rightarrow$ Tachycardia
  = **Sympathomimetic**
2-**Histamine like** $\rightarrow$ V.D., Bronchospasm & $\uparrow$ Gastric HCl
3-**Parasympathomimetic** $\rightarrow$ Bronchospasm & $\uparrow$ Gastric HCl
4-**Anti-serotonin**

2-**Therapeutic Uses**:
  a-Peripheral vascular diseases (PVD) e.g. Raynaud's disease
  b-Diagnose Pheochromocytoma, I.V. Phentolamine $\rightarrow$ Drop of Bl.p.
  c-V.C. & Hypertension due to sympathomimetics & withdrawal of clonidine
  d-Erectile dysfunction in males (Intracavernous Phentolamine + Papaverine)

3-**Contraindications**: Hypotension, Angina, Bronchial asthma & Peptic ulcer

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B) β-Haloalkylamines:

- **Phenoxybenzamine** *(Dibenzyline)*

1-**P**owerful, **P**artially selective ($\alpha_1 > \alpha_2$) α-blocker, **P**rodrug

2-Binds ***covalently*** with α-receptors $\rightarrow$ Irreversible non-competitive block

3-Slow onset (till activation)
  & long duration $\rightarrow$ 3-4 days (till resynthesis of new α-receptors)

4-Block *BOTH* neuronal uptake-1 & extraneuronal uptake-2

5-Anti-cholinergic (# M), Anti-histaminic (# H_1) & Anti-serotonin (# 5-HT)

6-**Useful in**:
  a-Pheocromocytoma
  b-Peripheral vascular diseases e.g. Raynaud's disease
  c-Benign Prostatic Hyperplasia (BPH)

7-**Side effects**:
  a-Sedation (# H_1)
  b- Dry mouth (# M)
  c- Flush & congestion (# α_1)
  d-Tachycardia (# M + # α_2 + ↓ Uptake + ↓ Bl.p)
  e-Failure of ejaculation
  e-Postural hypotension

*Selective α_2-Adrenoceptors Blocker:

♦ **Yohimbine** *(Yohimbex, Sex forte, Sex Vigor)*

1-Selective α_2-blocker →
  a- ↑ Release of Noradrenaline
  b-Does NOT reverse hypertension of Adrenaline
2- ↑ ADH release.
3-Local anesthetic
4-Aphrodesiac → Improve erection in male patients

NB) Drugs used in Erectile Dysfunction in Males:

1-Intracavernous Phetolamine + Papaverine

2-Intracavernous PGE-1 (Alprostadil)

3-Apomorphine PO → Nausea & vomiting

4-Yohimbine PO

5-**Sildenafil** *(Viagra 50 mg PO)* → ↓ Phophodiesterase-5 → ↑ cGMP → V.D. → Erection
6- **Tadalafil** *(Cialis 10 mg PO)* → Similar to Sildenafil ***BUT*** Longer duration.

Classification of Alpha Adrenoceptor Blockers

A) Selective α_1-Blockers:

1-Prazosin, Doxazosin, Terazosin & Alfuzosin
2-Tamsulosin
3-Indoramine

B) Non-Selective α_1 & α_2-Blockers:

1-Imidazoline Derivatives: Phentolamine & Tolazoline
2-β-Haloalkylamines: Phenoxybenzamine

They **Reverse** Hypertension of Adrenaline

C) Selective α_2-Blocker: Yohimbine → **NOT** reverse adrenaline hypertension

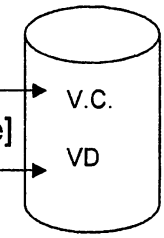
D) Drugs With α-Blocking Effect:

1-Ergot Alkaloids: Ergotamine & Ergotoxine
2-Labetalol & Carvedilol → β-Blockers
3-Chlorpromazine → Dopamine blocker & Anti-psychotic
4-Tricyclic anti-depressants e.g. Amitriptyline
5-Ketanserin: Anti-Serotonin

Ergot Alkaloids

- Lysergic acid derivatives
- Obtained from Ergot fungus that grows on Rye
- They include: Ergotamine, Ergotoxine & Ergometrine

*Pharmacological Actions of Ergot Alkaloids:



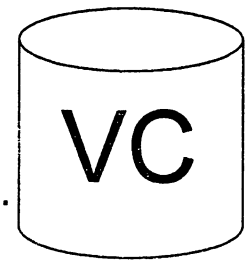
1-Direct SPASMOGENIC effect on smooth muscles:
- a-Blood vessels → V.C. *[Especially Ergotamine & Ergotoxine]*
- b-Uterus → Oxytocic effect *[Especially Ergometrin & **Methyl**-ergometrine]*

2-α-blocking effect → V.D. *Especially **Dihydro**-ergotoxine]*

3-C. N. S.: (٢ حلو ثم ٢ وحش ثم يجنن ويموت)
- a- ↓ V.M.C.
- b- ↑ C.I.C.
- c- ↑ C.T.Z.
- d-↓ Hear Regulating Center → Hyperthermia
- e-Psychological disturbances
- f- ↓ R.C.

4-**NB**:
- a-**Dihydrogenation** of Ergot → ↑ α-block & ↓ Spasmogenic → V.D. *[**Dihydro**-ergotoxine]*
- b-**Methylation** of Ergot → ↑ Spasmogenic effect *[**Methyl**-ergometrine]*

1-Ergotamine:



1-Potent Direct **Spasmogenic** Effect → B.V. → Powerful **V.C.**
→ Uterus → Oxytocic effect

2-**Partial Agonist** = Weak stimulation of α & 5-HT_{1D} receptors → **V.C.**

3-**C.N.S.**: ↑ C.I.C., ↑ C.T.Z., ↓ V.M.C. & ↓ R.C.

4-Therapeutic Use: ***Acute Migraine Headache***
- a-Better taken during First Stage (Aura): Oral, S.L., Rectal, Inhalation & Parenteral
- b-Better add Caffeine *[Cafergot]* → More V.C. & ↑ Absorption of Ergotamine
- c-Doses:
  - -Ergotamine : 1/4 - 1/2 mg, maximum 6 mg / attack or 10 mg / weak
  - -Cafergot [1 mg Ergotamine + 100 mg Caffeine]: Oral & Suppository

5-Side effects & Toxicity = ***Ergotism***
- a-Cold extremities, tingling, numbness & gangrene
- b-Hypertension & angina
- c-Nausea & vomiting
- d-Abortion

6-Contraindications:
- a-Peripheral Vascular disease
- b-Hypertension & Coronary heart diseases
- c-Pregnancy
- d-Liver & kidney disease

NB) Drugs &Receptors:

1-Agonist: Affinity + Efficacy → ↑Receptor

2-Antagonist: Affinity + NO Efficacy → Block Receptor

3-Partail Agonist (Dualist):
Affinity + Weak Efficacy:
a-Alone → Weak stimulation of receptors
b-With agonist → Block effect of agonist

NB) ***Dihydro-ergotamine***., similar to ergotamine *& can be given I.M. & I.V.*

2-Dihydroergotoxine *(Hydergin)*:

1-More α-block & ↓ V.M.C. → V.D. → Useful cerebral & peripheral ischemia
2- ↑ C.T.Z. → Nausea

3-Ergometrine = Ergonovine & Methyl-ergometrine *[Methergin]*

1-*Poserful* **Oxytocic**, *weak* ***V.C.***, ***NO*** α-block or CNS actions
2-Uses:
a-Treat postpartum hemorrhage (after delivery of fetus & placenta)
b-Help involution of uterus
c-Diagnose Variant [Prinzmetal angina] → Ischemic heart changes in ECG

NB] Ergot Alkaloids & Related Drugs:

A) Natural Ergot Alkaloids:

1-Amino acid alkaloids: Ergotamine & Ergotoxine
2-Amine alkaloids: Ergometrine (Ergonovine)

B) Semi-synthetic Ergot alkaloid Derivatives:

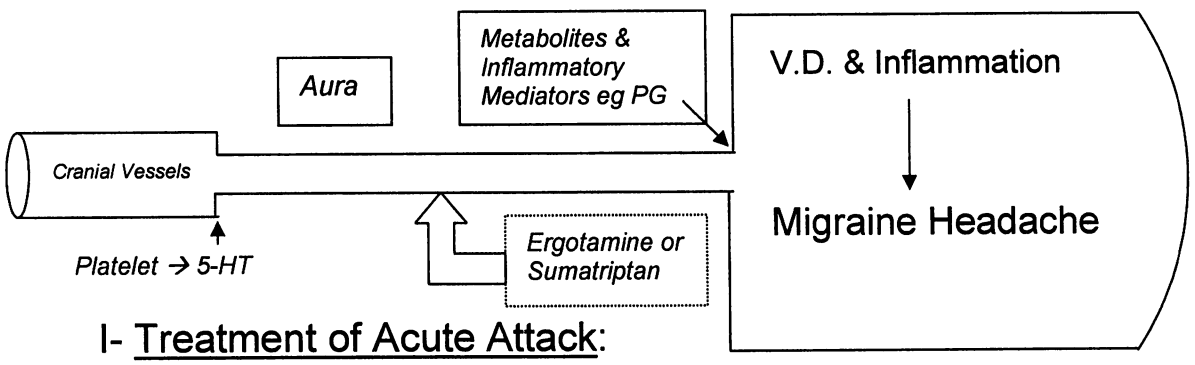
1-Dihydroergot amine 2-Dihydroergotoxine 3-Methylergometrine

4-Lysergic Acid Diethylamide (LSD) → D-agonist & 5-HT antagonist → Hallucinogenic

5-Bromocriptine → Dopamine agonist: → Antiparkinsonian & ↓ Prolactin

6-Methysergide → Anti-serotonin → Prophylaxis of Migraine headache

NB] Migraine Headache:



I- Treatment of Acute Attack:

- Non-pharmacological methods are not sufficient without concomitant drug treatment.
- Adequate doses of drugs as early as possible.
- Oral absorption may be impaired due to gastric stasis. Either:
  - Use prokinetic agent e.g. Metoclopramide.
  - Other routes may be tried such as rectal and parenteral.

A) Mild Attacks → Simple Analgesic + Antiemetic + Sedative:

1- Adequate in 90% of cases.

2- **Simple Analgesic**:
   a- Paracetamol 500 mg
   b- NSAID e.g. Aspirin 600 mg → Analgesic + ↓ Platelet aggregation.

3- **Antiemetic**: Metoclopramide → Antiemetic + Prokinetic → ↑ Absorption of other drugs.

4- **Sedative**: Diazepam →
   a- Emotional stress-triggered attacks.
   b- Sleep is an important remedy in treatment.

B) Severe Attacks → Ergotamine (See before) or Sumatriptan

1-Ergotamine ± *Metoclopramide* ± *Caffeine* ± *Simple analgesic* *(Amigraine, Migrainil, Metograine, N0-Migraine, Stopain, Spasmomigraine)*

2-**Sumatriptan** *(Imigran, Sumagrain)*:

1-*5-HT_{1D}* partial agonist → VC.

2-Highly *effective*, but *expensive* & short acting < 12 hours

3-*Dosage*: Oral 100 mg (max 300 mg/day) & SC 6 mg (max 12 mg/day).

4-*Side Effects*:

a-Drowsiness, fatigue & malaise.
b-Nausea & vomiting.
c-Anginal pain & hypertension.
d-Muscle pain.

5-*Contraindications*:

a- PVD b- Hypertension c- Coronary heart disease.
d- Liver & Kidney diseases e- Pregnancy.

6-*Drug Interactions*:

a-MAO.I. or SSRI → Serotonin reaction.
b-Ergotamine & dihydroergotamine → Severe VC.

II- Prophylactic Treatment:

- If > 2 attacks/month.
- Adjustment of life style and diet.
- Lag about 2 weeks.
- ***Avoid*** precipitating drugs e.g. ***Reserpine & Oral contraceptives***

1-**Methysergide** *(Deseril)* : 4-12 mg/day Orally

a-Lysergic acid derivative, related to Ergot alkaloids.
b-Strong 5-HT_2 antagonist.
c-Allowed in pregnancy.
d-Long use > 6 months→ Retroperitoneal fibrosis.

2-**Pizotifen**:

a-Anti-serotonin, anti-histamine & anti-cholinergic.
b-Side Effects : Sedation, ↑ appetite & dry mouth.

3-**Cyproheptadine** *(Periactin)* : Similar to pizotifen.

4-**β-Blockers**: Propranolol (60-240 mg/day Orally) & Metoprolol.

a-May be due to membrane stabilization & antagonism of VD.
b-Ergotamine (in acute attack) + Propranolol (prophylaxis) → Severe VC.

5-**Clonidine** in S.D. 0.025-0.05 mg bid PO. An α_2-agonist → ↓ Sympathetic.

6-**Calcium channel blockers** e.g. Flunarizine *(Sibelium)*

7-**Tricyclic antidepressants** e.g. Amitriptyline

8-**Sedatives & Tranquilizers** e.g. Diazepam.

9-**Premenstrual migraine** may respond to a simple analgesics + a diuretic.

Beta - Blockers

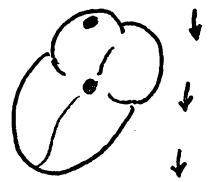
Actions	Uses	Adverse Effects & Contraindications
1- Heart (β_1): -ve Inotropic -ve Chronotropic -ve Dromotropic ↓ COP ↓ Cardiac work & O_2 consumption ↓ Excitability & ↓ Automaticity	Hypertrophic obstructive cardiomyopathy Tachycardia e.g. Thyrotoxicosis Atrial tachyarrhythmia → Protect ventricles Angina of Effort Arrhythmia	Heart failure Bradycardia Heart block } NOT with Verapamil Variant (Prinzmetal) angina
2- Blood vessels (β_2): ↓ V.D. → Unopposed α → V.C.		P.V.D.
3- Anti-hypertensive: ↓ Sympathetic outflow from CNS ↓ COP ↓ Renin ↓ Noradrenaline release Reset Baroreceptors ↑ PG	Hypertension + α-blockers in Pheochromocytoma	Hypotension Alone in Pheochromocytoma
4- ↓ I.O.P.:	Glaucoma (Timolol)	Practolol → Muco-Cutaneous-Ocular syndrome
5- Bronchi (β_2) → Bronchospasm		Bronchial asthma
6- Metabolism: ↓ β_2 → ↓ Glycogenolysis ↓ β_2 → ↓ Hypokalemia ↓ β_1 & β_3 → ↓ Lipolysis		With insulin → Severe hypoglycemia Hyperkalemia ↑ Triglycerides & ↓ H.D.L.
7- I.S.A. (Some β-Blockers) = Dualist		
8- C.N.S. (Lipophilic β-Blockers) ↓ Anxiety ↓ Tremors	Migraine headache (Propranolol) Anxiety & Panic syndrome Familial tremors	Sedation
9- Na^+ Channel Block (Some β-Blockers): Membrane stabilizer = Local anesthetic Direct Myocardial Depressant		Sudden Stop

Beta-Adrenoceptor Blockers

* Pharmacodynamics:

I- Beta – Blocking Effects:

A) Heart (β_1 Mainly & some β_2):



1- -ve Inotropic effect = ↓ Contractility.
2- -ve Chronotropic effect = ↓ Heart rate
   a-Block mainly exercise- & anxiety-induced tachycardia.
   b-Minimal effect on resting heart rate due to vagal predominance.
3- -ve Dromotropic effect = ↓ A-V conduction → Useful in Atrial tachy-arrhythmia.
4- ↓ COP.
5- ↓ Cardiac work & ↓ O_2 needs of myocardium → Useful in Angina of Effort
6- ↓ Excitability & Automaticity → Anti-arrhythmic (Class II).

B) Blood Vessels (β-2):

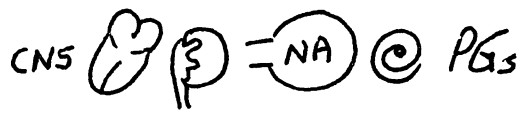
1- Non-selective β-blockers → Block Sk.m. VD induced by adrenaline & isoprenaline.
   Block **hypo**tensive effect of Isoprenaline & *augment* **hyper**tension of Adrenaline
2- VC may occur due to unopposed α-receptor activity:
   a- Initial ↑ Total Peripheral Resistance (↑ TPR).
   b- ↓ Blood flow to ALL organs Except the brain:
      - Cold extremities & intermittent claudication.
      -↓ Hepatic blood flow by 30% → Enzyme inhibition.

3-After long use β-Blockers ↓ TPR (↓ Sympathetic tone, ↓ Renin, ↓ N.A. & ↑ PG)

C) Blood Pressure:

Anti-hypertensive effect after LONG oral use > 4 Weeks :

1-Block β-1 of CNS → ↓ Sympathetic outflow
2-Block β-1 of Heart → ↓ COP.
3-Block β-1 of Kidney → ↓ Renin.
4-Block Pre-synaptic β → ↓ Release of N.A.
5-Resetting the sensitivity of Baro-receptors.
6-↑ Prostaglandins (PGI_2)



-β-blocker ↓ TPR after long use

D) Eye:

1- ↓ IOP: ↓ Aqueous humor formation, after Oral & Local use (*specially Timolol).*
2- They do NOT affect pupil size or ciliary muscle or accommodation.

E) Bronchi:

Non-selective β-blockers → BronchoSPASM especially in asthmatic patients.

F) Metabolism: 

1- Block β-2 in Liver → ↓ Glycogenolysis → Hypoglycemia.
2- Block β-2 in Pancreas → ↓ Release of Insulin.
3- Block β-2 in Sk.m. → Block Hypokalemic phase induced by Adrenaline.
4- Block β-1 & β-3 in Adipose tissues → ↓ Lipolysis.
β-Blockers → ↑ Triglycerides & ↓ HDL.

II- Some β-Blockers Have Intrinsic Sympathetic Activity (ISA) = Partail Agonistic Activity = Partial Agonist = Dualist *(Affinity but weak efficacy):*

1-Harmful in patients with supersensitive β-receptors e.g. Thyrotoxicosis.
2-Useful:
a- β_1-partial agonistic activity → Less cardiac inhibition.
b- β_2-partial agonistic activity → Less bronchospasm.
c- Less metabolic disturbances especially on lipids.
d- Less upregulation of β-receptors → Less Supersensitivity & Less withdrawal rebound effects.

NB) Drugs &Receptors:

1-Agonist: Affinity + Efficacy → Stimulate the Receptor

2-Antagonist: Affinity + NO Efficacy → Block the Receptor

3-Partail Agonist (Dualist): Affinity + Weak Efficacy:
a-Alone → Weak stimulation of receptors
b-With agonist → Block effect of agonist

III- CNS Effects:

Some β-blockers → Lipophilic e.g. Propranolol → Pass BBB → ↓ Anxiety & ↓ Tremors

IV- Cell Membrane Stabilization:

1- Some β-Blockers → Block Na^+-channel:
2- Direct myocardial depressant = Quinidine-like effect.
3- Local anesthetic effect.

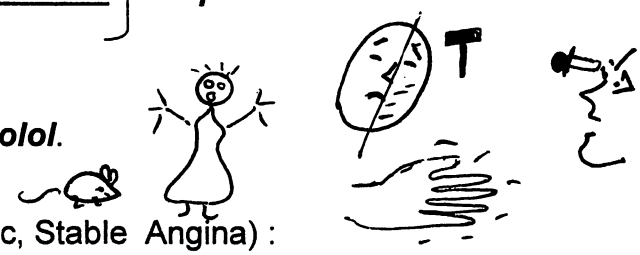
* Therapeutic Uses of β-Blockers :

The dose of β-Blocker is adjusted by keeping:
1- Resting Heart Rate = 55-60 beats/min.
2- Maximum exercise-induced tachycardia = 100-120 beats/min.

I- CNS:

1- ***Anxiety & Panic*** disorders
2- Drug of CHOICE in ***Essential Familial Tremors***.
3- Prophylaxis of ***Migraine*** headache.

Lipophilic β-Blockers e.g. ***Propranolol***



II- Eye : ***Open Angle Glaucoma*** :

- Topical ***Timolol, Betaxolol & Levobunolol.***

III- Heart :

1- ***Angina Pectoris*** (Effort, Exertion, Classic, Stable Angina) :
   a- β-Blockers do NOT produce coronary VD or ↑ coronary flow.
   b- ↓ Cardiac work = ↓ Oxygen needs of myocardium.
   c- -ve Chronotropic :
      - Long diastolic filling of coronaries.
      - Prevent exercise and anxiety induced tachycardia.
      - Prevent tachycardia of other anti-anginal drugs e.g. Nitrates & Nifedipine.
   d- Long use → Anti-hypertensive effect → ↓ TPR → ↓ After-load.
      However, due to bradycardia → Long diastolic filling → ↑ EDV → ↑ Preload.
   e- Redistribution of coronary flow to the ischemic area.

2- Early phase of Mild ***Myocardial infarction*** → ↓ Mortality rate.

3- ***Cardiac Arrhythmias*** (Atrial & Ventricular):
   More useful in Atrial arrhythmia : ↓ A-V conduction → Protection of Ventricles.

4- ***Thyrotoxicosis*** : Better use β-blockers withOUT ISA due to supersensitivity :
   a- Treat tachycardia & ↑ cardiac work of thyrotoxicosis.
   b- ***Propranolol*** ↓ peripheral deiodination of T_4 to the more active T_3.

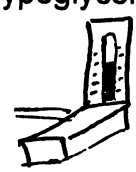
5- ***Heart Failure***:
   a- Small doses of selective β_1-blockers e.g. ***Metoprolol, Bisoprolol & Carvedilol*** (β_2-agonist + Anti-oxidant) → ↓ Mortality rate in Heart failure
   b- Protect the heart from the cardiotoxic effect of high catecholamine and renin-angiotensin activity that occur in heart failure

6- ***Hypertrophic obstructive cardiomyopathy***. β-blockers may ↑ COP.

IV- Blood Pressure & Vessels :

1-***Hypertension*** : Better avoid in pregnancy → Fetal bradycardia & hypoglycemia.

2-With α-blockers in ***Pheochromocytoma***. Never alone.



3-***Portal hypertension & Esophageal varices***.

4-***Acute dissecting aortic aneurysm***.

*Adverse Effects of β-Blockers:

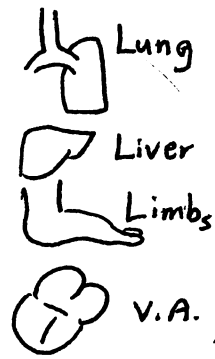
1- C.N.S.: Sedation, depression & sleep disturbances

2-Eye: ***Practolol*** → Muco-Cutaneous-Ocular Syndrome

3-Heart:

a- -ve Inotropic → Heart failure *(Treat by Digitalis or Glucagon)*
b- -ve Chronotropic → Bradycardia } *- Treat by Atropine*
c- -ve Dromotropic → Heart Block } *- Never combine with Verapamil*

4- Block β_2-Receptors *(Non-Selective β-Blockers):*



a-Bronchospasm & precipitate bronchial asthma *(Treat by Theophylline)*
b- ↓ Hepatic glycogenolysis → Hypoglycemia
Avoid with Insulin → Symptomless Hypoglycemic coma.
In diabetic patients, selective β_1-blockers are allowed with caution
c- ↓ Blood flow to organs *(Except the Brain)*:
- ↓ Hepatic blood flow → ↓ Metabolism
- Limbs → Cold extremities & Intermittent claudication
- Coronary V.C. → Avoid in Variant (Prinzmetal Angina)

5-G.I.T.: Disturbances

6- Sexual dysfunction in male patients

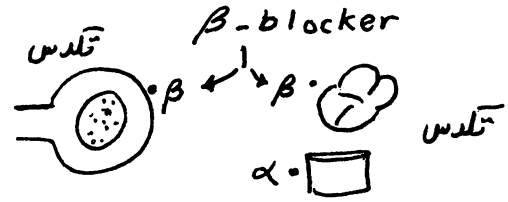
7-Metabolism:

a-Augment hypoglycemia of insulin
b-↑ Triglycerides & ↓ H.D.L.
c-Block Hypokalemia → Hyperkalemia specially during muscle exercise

8-Hypersensitivity = Allergy

9-***Sudden Stop*** of β-Blocker therapy → Rebound β-Stimulation *(Up-regulation of adrenoceptors)* → Severe Tachycardia, Arrhythmia & Hypertension → Dangerous

*Contraindication of β-Blockers:



1-Block of β_1:

a-Heart block
b-Heart failure (Avoid Large doses)
c-Hypotension

2-Block of β_2 (Non-Selective β-Blockers): *S.D. of selective β_1-blckers are allowed with caution*

a-Variant (Prinzmetal) angina
b-Peripheral vascular diseases
c-Alone *(Without α-blockers)* in Pheocromocytoma
d-Bronchial asthma
e-Diabetes mellitus

3-***Sudden Stop*** of β-Blocker Therapy

*Drug Interactions of β-Blockers:

1-Enzyme induces e.g. Phenytoin & Tobacco smoking → ↑ Their metabolism
2-Enzyme inhibitors e.g. Cimetidine → ↓ Their metabolism
3-β-Blockers → ↓ Hepatic blood flow → ↓ Metabolism of lidocaine & their own
4-Verapamil & Diltiazem → Severe cardiac inhibition
5-NSAID (↓ PG syntheisi) → Antagonize antihypertensive effect of β-Blockers
6-Augment hypertension of adrenaline & Clonidine withdrawal
7-Augment hypoglycemia of insulin & Sulphonylurea hypoglycemics

*Classification of β-Blockers:

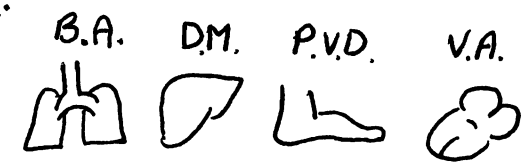
A) According To Selectivity:

	Receptors Blocked	ISA	Na^+-Block = Local Anesth	Hepatic Metabolism	Remarks
A) Non-Selective:	$\beta_1 + \beta_2$				C.I. in V.A., B.A., D.M. & P.V.D.
1- Oxprenolol		+++	+++	Extensive	P.A. "Dualist" ⎫ Not suitable in
2- Pindolol		+++	±	+	P.A. "Dualist" ⎭ Hyperthyroidism
4- Propranolol		NO	+++	Extensive	Extensive first pass effect
5- Sotalol		NO	NO	NO	Renal, Class II Antiarrhythmic
6- Nadolol		NO	NO	NO	Renal, Long, Low lipid, Little CNS
7- Timolol		NO	NO	+	Glaucoma
B) Cardio-Selective:	β_1				Allowed SD with caution in V.A., B.A., D.M. & P.V.D.
1- Atenolol		NO	NO	NO	Renal Long, Low lipid, Little CNS
2- Bisoprolol		NO	NO	+	Long acting
3- Betaxolol		NO	NO	+	Glaucoma
4- Metoprolol		NO	NO	Extensive	
5- Esmolol		NO	NO	RBC estrase	Ultrashort → IV Infusion
6- Acebutolol		+++	+++	+	Dualist
7- Celiprolol	β_1	β_2	NO	NO	V.D. β-Blocker
8- Nebivolol	β_1		NO	NO	↑ Nitric oxide → V.D. β-blocker
C) Selective β_2: Butoxamine					
D) α + β Blockers:	$\alpha_1 + \beta$				V.D. β-Blockers
1- Labetalol ----------	----------	B_2			
2- Carvedilol ----------	----------	β_2	----------	----------	Antioxidant
3- Bucindolol					
4- Medroxalol					

B) According to Lipid Solubility = Pharmacokinetics:

	Lipophilic	Lipophobic = Hydrophilic
1-Examples:	- Propranolol - Oxprenolol - Metoprolol	- Nadolol - Atenolol - Sotalol
2-GIT Absorption	Well absorbed	Less
3-B.B.B.	Pass → CNS actions	Less
4-Hepatic Metabolism	Rapid Metabolism	Less, mainly RENAL
5-Duration	Short Duration → tds	Longer duration → od

*Members of β-Blockers:



A) Non-Selective β-Blockers:

- Block BOTH β_1 & β_2 receptors
- Lung → Bronchospasm → Contraindicated in Bronchial asthma (B.A.)
- Liver → ↓ Hepatic blood flow & ↓ Glycogenolysis → C.I. in Diabetes mellitus (D.M.)
- Limbs → ↓ Blood flow → C.I. in P.V.D. e.g. Raynaud's disease
- Coronary → C.I. Variant (Prinzmetal) angina (V.A.)

1- Oxprinolol *(Trasicor)*
2- Pindolol *(Visken)*
} - Powerful β-Blockers
- Have I.S.A. = Dualist or Partial agonist
- Not suitable in supersensitivity e.g. Hyperthyroidism

3- Propranolol *(Inderal)*

1-NO I.S.A. → Antagonist → Useful in Supersensitivity e.g. Hyperthyroidism. It also inhibits the deiodination of T-4 to more active T-3.
2-Blocks Na^+-Channel → Membrane stabilizer = Local anesthetic = Direct Myocardial Depressant
3-Extensive Hepatic First Pass Metabolism (75%) → Low (25%) Oral Bioavailability. Oral dose 10–80 mg tds while I.V. dose 0.5–3 mg. Start by S.D. then ↑ gradually.
4-Extensive (90-95%) bound to plasma proteins

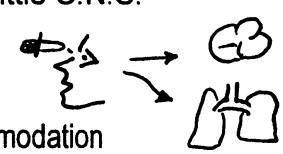
4- Sotalol *(Betacor)*: 80 mg bid

1-No I.S.A. 2- No L.A. 3-No Hepatic metabolism
4-Renal Excretion 5-Class II Antiarrhythmic

5- Nadolol *(Corgard)*: 80 mg od

1-No I.S.A. 2-No L.A. 4-No Hepatic metabolism
5-Renal Excretion 6- Long duration 6-Low lipid solubility 7-Little C.N.S.

6-Timolol *(Timoptec)*



1-No I.S.A. 2- No L.A. 4-Hepatic metabolism
5- ↓ Aqueous humor formation → ↓ IOP without change in pupil size or accommodation
6-Eye drops (0.25 – 0.5 %) in treat of chronic open angle glaucoma
7-Absorbed from eye → Affect heart & Bronchi → C.I. in H.B., H.F. & B.A.

B) Cardio-selective β_1-Blockers:

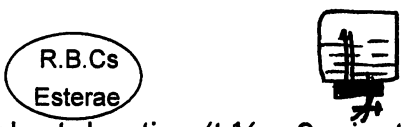
♦ Allowed in small dose with caution in V.A., B.A., D.M. & P.V.D.

1-Atenolol *(Tenormin, Ateno, Atelol, Blokium, Tenosolol)*: 50 – 100 mg od
1-No I.S.A. 2-No L.A. 4-No Hepatic metabolism
5-Renal Excretion 6-Long duration 6-Low lipid solubility 7-Little C.N.S.

2-Bisoprolol *(Concor)*: 5 – 10 mg od
1-More selective β_1-block than Atenolol.
2-No I.S.A. 3-No L.A. 3-Long duration

3- Metoprolol *(Lopressor, Betaloc)*: 100 mg bid
1-No I.S.A. 2-No L.A.

4- Esmolol *(Brevibloc)*: I.V. Infusion
1-No I.S.A. 2-No L.A.



3-Rapid hydrolysis by RBC's esterase → Ultrashort duration (t ½ = 9 minutes)

5-Acebutolol *(Sectral)*: 400 – 800 mg / day
1-Has I.S.A. = Dualist or partial agonist 2- Has Local anesthetic activity

C) Selective β_2-Blocker: ***Butoxamine*** → Experimental agent

D) Vasodilator β-Blockers:

1- β_1-Block + β_2-Partial agonist:

-Celiprolol: No I.S.A. & No L.A.

2-β_1-Block + Nitrogenic:

- **Nebivolol:** Selective β_1-block + ↑ Production of Nitric Oxide

2- α + β - Blockers:

a-Labetalol *(Trandate)*: 100 – 400 mg tds
- α_1-Block + β-Block (β-Blocker *more than* α-Blocker) + β_2-Partial agonist
- Weak as α-blocker (< Phentolamine) & weak as β-blocker (< Propranolol)
-Potent hypotensive: ↓ T.P.R. (α-blocker) & ↓ Renin (β-blocker)
-Minimal change in Heart rate & C.O.P.
-Useful in treatment of emergency hypertension & Pheochromocytoma

b-Carvedilol *(Dilatrend)*: Similar to *Labetalol* + ***Antioxidant*** (6.25-25 mg)

c-Bucindolol

d-Medroxalol

Adrenergic Neuron Depressants

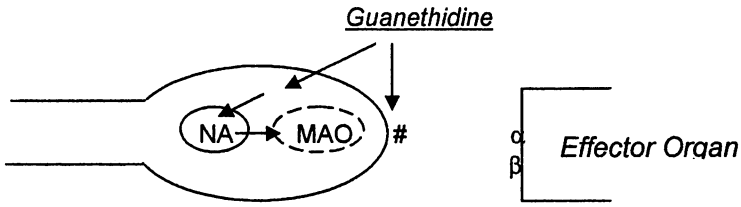
1-Guanethidine *(Ismelin)*

Synthetic Sympathoplegic Hypotensive Drug

*Pharmacokinetics:

1- Absorption: Incompletely absorbed orally → Variable bioavailability
2- Distribution: Does ***NOT*** pass B.B.B. or Adrenal medulla
3- Uptake and store by adrenergic nerve endings
4- Slow renal excretion
5- Slow onset (2-3 days) & Long duration (7-10 days) → Cumulative

*Pharmacodynamics: ↓ Release of Noradrenaline (NA)

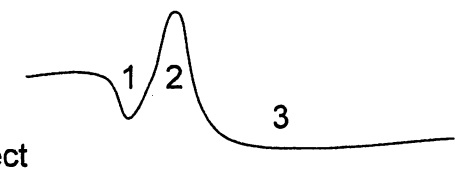


- **Mechanism of Action:** *↓ Release of Noradrenaline (↓ Exocytosis)*

1- Guanethidine undergoes Active Neuronal Uptake-1 (similar to Noradrenaline).
2- Then granular uptake
3- Initial release of Noradrenaline → Metabolized by M.A.O. → Depletion
4- Inhibit the release of endogenous Noradrenaline in response to nerve action potential (↓ Exocytosis) = Adrenergic neuron blocker → ↓ Sympathetic activity.
5- Guanethidine ↓ Neuronal uptake-1 of Exogenous Noradrenaline → Supersensitivity
6- Guanethidine does ***NOT*** affect C.N.S. or Adrenal medulla.

- **Pharmacological Actions:** *[↓ Sympathetic → As if → ↑ Parasympathetic)*

1- C. V. S.:



a- Hypotension & Postural hypotension
b- If I.V. injection → Triphasic effect on Bl.p.
  - Initial hypotension due to direct vasodilator effect
  - Transient hypertension due to initial release of Noradrenaline
  - Prolonged hypotension due to ↓ release of Noradrenaline
c- Bradycardia → ↓ C.O.P. → ↓ R.B.F. → Fluid retention → Edema
d- V.D. of skin & mucous membranes → Flush & nasal congestion

2- Eye: Miosis, ↓ I.O.P.

3- G.I.T.: Parotid pain & congestion and ↑ Motility & ↑ Secretion → Diarrhea

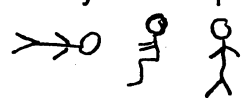
4- Geneto-urinary: Failure of ejaculation (No impotence)

* Therapeutic Uses of Guanethidine:

1- Hypertension especially in patients with Psychic depression or Parkinsonism
2- Eye drops in Glaucoma & to ↓ Exophthalmia of Thyrotoxicosis

* Dosage of Guanethidine:

1- Start by 10 mg/day increase by 10 mg every 10 days till control of blood pressure or maximum dose of 100 – 300 mg/day
2- Measure Bl.p while recumbent, sitting & standing the difference in systolic Bl.p. must not exceed 25 mmHg → To avoid postural hypotension



*Adverse Effects of Guanethidine:

1- *C.V.S.*: ***Postural (Orthostatic) & Exertional hypotension***, bradycardia, fluid retention, flush and nasal congestion
2- *G.I.T.*: Parotid pain & congestion and diarrhea
3- Failure of ejaculation.

*Contraindications of Guanethidine: *Pheochromocytoma*

*Drug Interactions of Guanethidine:

1- Supersensitivity to exogenous catecholamines
2- Cocaine & Tricyclic antidepressants → ↓ Neuronal uptake of Guanethidine
3- Reserpine & Amphetamine → ↓ Storage of guanethidine in adrenergic vesicles

NB) ***Bretylium***: Similar to guanethidine, used mainly as Class III Antiarrhythmic

2- Reserpine *(Serpasil)*

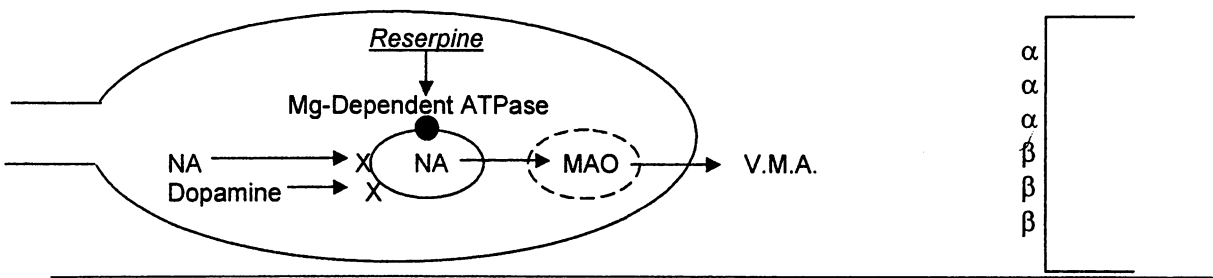
Natural Sympathoplegic, Hypotensive and Major tranquillizer; Rawoulfia alkaloid

*Pharmacokinetics:

1- Absorbed orally 2- *Passes B.B.B. and adrenal medulla* 3- Excreted in urine

*Mechanism of Action:

Depletes 2 → *Catecholamine & Serotonin* ***from 2*** → *C.N.S. & Periphery*



*Mechanism of Action of Reserpine:

1- Reserpine ↓ Granular uptake without affecting neuronal uptake-1.
2- It ↓ irreversibly specific granular enzyme (Mg^{2+} dependent ATPase) responsible for storage of NA, and granular uptake of NA & Dopamine (↓ synthesis of NA) → **Depletion** of **Catecholamines** in CNS & Periphery → ↑ Urinary VMA.
3- A sort of denervation supersensitivity occurs (Upregulation of receptors)
4- The same occurs with **Serotonin** stores in CNS & Periphery → ↑ Urinary 5-HIAA
5- The effect of reserpine ends by ***resynthesis*** of new granules (7-10 days).

*Pharmacological Actions of Reserpine:

A) C.N.S.:

1- Depletion of catecholamines (Noradrenaline & Dopamine) & Serotonin →
a-Major tranquillization (Anti-psychotic)
b-Sedation, Psychic depression & Nightmares → Suicidal ideations
c-Parkinsonism

2- ↓ V.M.C. → ↓ Sympathetic & ↑ Vagal C.I.C. → ↑ Parasympathetic

B) Eye: Miosis

C) C.V.S.:

1- Hypotension: Central (↓ VMC & ↑ CIC) & Peripheral (depletion of catecholamines)
2- Bradycardia → ↓ C.O.P. → ↓ R.B.F. → Fluid retention → Edema
3- Skin & mucous membranes V.D. → Flush and nasal congestion

D) G.I.T.:

1- ↑ Secretions e.g. HCl → Peptic ulcer
2- ↑ Motility (May be through release of Serotonin) → Diarrhea
3- ↑ Appetite

E) Endocrine: ↑ Prolactin → Galactorrhea, Gynecomastia & Impotence

*Therapeutic Uses of Reserpine:

1- Hypertension (NO Psychic depression or Parkinsonism) 0.1 –0.25 mg po
2- Psychosis e.g. Schizophrenia up to 10 mg/day

*Adverse Effects of Reserpine:

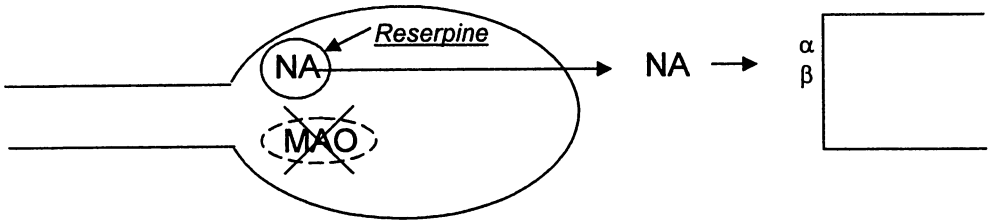
1- *C.N.S.*: Sedation, Psychic depression, nightmares, suicidal ideation & Parkinsonism
2- *C.V.S.*: Bradycardia, Fluid retention, flush and nasal congestion
3- *G.I.T.*: Peptic ulcer, diarrhea
4- Weight gain (↑ Appetite & Fluid retention)
5- Endocrine → ↑ Prolactin → Galactorrhea, Gynecomastia & Impotence

*Contraindications of Reserpine:

1- Psychic depression 2- Parkinsonism 3- Peptic ulcer

*Drug Interactions of Reserpine:

1- Supersensitivity to exogenous catecholamines
2- MAO inhibitors → Reserpine reversal → Excitation and hypertension[2].
3- General anesthesia → Severe hypotension difficult to control (supersensitivity), Stop reserpine 10 days before general anesthesia.



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Central Sympathoplegic Drugs

♦ Central α_2-Agonists → ↓ Sympathetic outflow + Sedation
♦ Central Imidazoline I_1-receptor Agonists → ↓ Sympathetic outflow + LESS Sedation

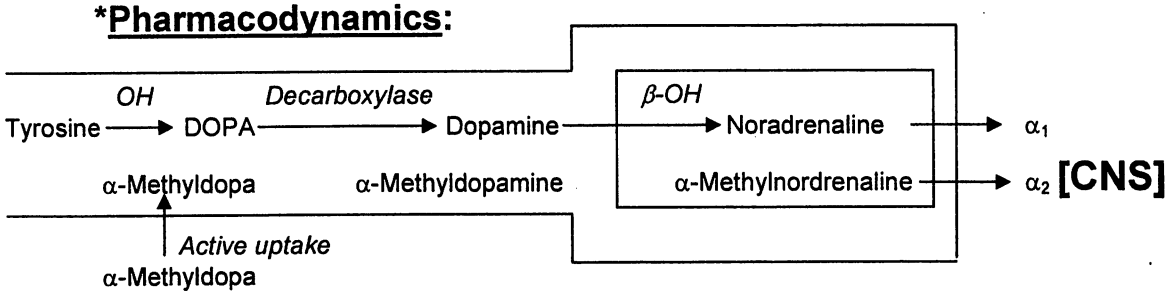
1- Alpha Methyl-Dopa (Aldomet)

Synthetic Central Sympathoplegic Hypotensive drug

*Pharmacokinetics:

1- Absorbed orally but Low oral bioavailability (25%)
2- Distributed all over the body & passes B.B.B.
3- ***Prodrug***, in periphery and CNS → Active neuronal uptake of α-Methyl-DOPA *(By Dopa decarboxylase)* → α-Methyl-dopamine (*By Dopamine β-hydroxylase*) → α-Methylnoradrenaline → α_2-Agonist

*Pharmacodynamics:

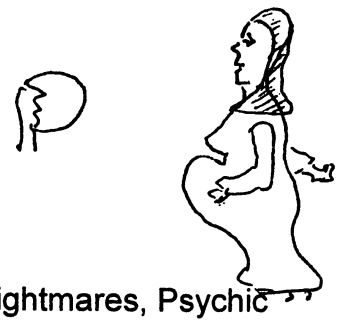


Antihypertensive effect by ***Central Sympathoplegic*** action:

CNS

1- *Main Mechanism*: ↑ central α_2 → ↓ Sympathetic out flow from C.N.S. → ↓ Heart rate, ↓ C.O.P. & ↓ T.P.R. → ↓ Bl.p.
2- ↑ Presynaptic α_2 → ↓ Release of Noradrenaline
3- ↑ Renal α_2 → ↓ Release of Renin
4- Occupies dopa decarboxylase enzyme → ↓ Synthesis of catecholamines & serotonin

*Therapeutic Uses of α-Methyldopa:



Hypertension (250 mg tds up to 2 g/day) especially:
1- Renal impairment (It ↑ R.B.F.)
2- Pregnancy (It is safe on fetus)

*Adverse Effects of α-Methyldopa:

1- *C.N.S.* → ↓ Catecholamines & Serotonin → Sedation, Nightmares, Psychic depression & Parkinsonism (less than reserpine)
2- *C.V.S.*: Bradycardia & fluid retention (*Due to VD of efferent renal arterioles → ↓ Glomerular pressure → ↓ G.F.R.*) → Hypervolemia → Antagonize the Anti-Hypertensive effect → ***Pseudotolerance*** # by Diuretics.

3- *G.I.T.*: Xerostomia & Constipation (↑ α_2 → ↓ Release of A.Ch. or CNS action)
4- *Endocrine* → ↑ Prolactin → Galactorrhea, Gynecomastia & impotence
5- *Allergy (Hypersensitivity)* → Fever, Hemolysis (+ve Coombs' test), Bone marrow inhibition & Hepatotoxicity

NB) ***Prodrugs***: Dipivefrin, l-DOPA (in Parkinsonism), Hexoprenaline, Phenoxybenzamine & α-Methyldopa.

2- Clonidine *(catapres)*

Synthetic, Central Sympathoplegic, Hypotensive, Imidazoline derivative

*Mechanism of Action:

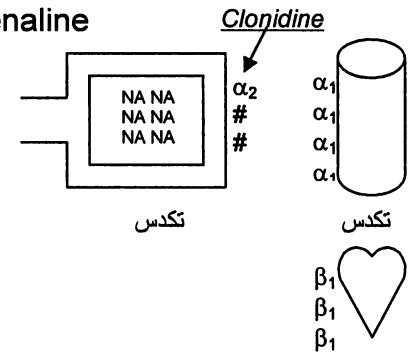
1- Antihypertensive effect:
   a- *Stimulate central* α_2 & Imidazoline I_1-receptors → ↓ Central sympathetic outflow from CNS → ↓ Sympathetic → ↓ H.R., ↓ C.O.P.& ↓ T.P.R. → ↓ Bl.p.
   b- ↑ Presynaptic α_2 → ↓ Noradrenaline release
   c- ↑ Renal α_2 → ↓ Renin release
2- Cerebral V.C. (↑ Postsynaptic α_2-adrenoceptors)

*Therapeutic uses:

1- Hypertension: Especially in patients with renal impairment
   Orally (Catapres 0.1 mg bid) or Transdermal patch/week (Catapress TTS)
2- Prophylaxis of Migraine headache: Orally (Dixrit 0.025 mg bid)
3- Diagnosis of Pheochromocytoma (Clonidine suppression test)
4- Control withdrawal symptoms of opioid (morphine) & Tobacco smoking
5- Control menopausal syndrome (Flushes)
6- Intrathecal as an analgesic

*Adverse Effects of Clonidine:

1- Large dose or I.V. injection → ↑ Postsynaptic α_2 → V.C. → Initial hypertension
2- Sudden stop of therapy → Sudden release of Noradrenaline
→ Severe hypertension (Pheochromocytoma like).
Treat by reusing clonidine or α-blocker ± β-blocker
(*But never β-blocker alone* → Augment hypertension).
3- C.N.S.: Sedation
4- C.V.S.: Bradycardia
5- G.I.T.: Xerostomia & constipation
6- Endocrine : Impotence



NB) Guanfacine *(Estulic, Tenex)*

α_2-Agonist similar to Clonidine BUT:
1-*Less* Sedation 2-Longer duration → *Less* withdrawal hypertension

NB) Guanabnz *(Wytensin)*

α_2-Agonist similar to Clonidine BUT has a *Diuretic* effect → Less pseudotolerance

NB) Anti-Renin:

1- β_1-Blockers: Selective (Atenolol), Non-selective (Propranolol) & α+β blocker (Labetalol)
2- α_2-Agonists: α-methylnoradrenaline & Clonidine

NB) Other α_2-Agonists:

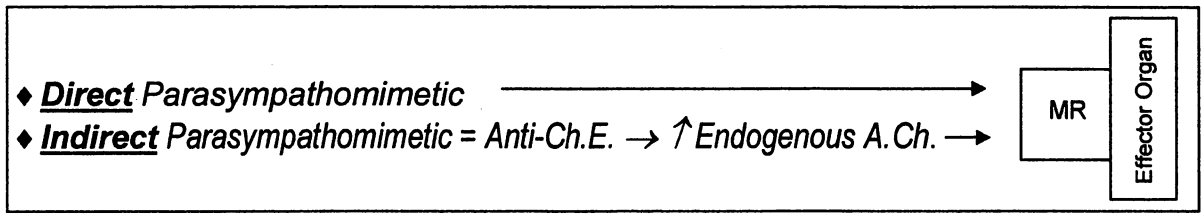
1- **Tizanidine** *(Sirdalud, Roysan, S.M.R.)* → Central muscle relaxant
2- **Apraclonidine** *(Iopidine)* & **Brimonidine** *(Alphagan)*→ ↓ Aqueous humor formation → ↓ IOP → Treat glaucoma

NB) Other Imidazoline I_1-Receptor Agonists:

↓ Sympathetic outflow from CNS *BUT* less sedative than α_2-agonits
1- **Moxonidine** *(Cynt 0.2 – 0.4 mg po od)*
2- **Rilmenidine** *(Hyperium 1 mg po od)*

Parasympathomimetics
(Cholinomimetics , Muscarinic-Receptor Agonists)

These are drugs that stimulate ***Muscarinic*** "Peripheral Cholinergic" Receptors (MR or PCR) either directly or indirectly:



Choline Esters

- ♦ Direct parasympathomimetics
- ♦ Contain ***Choline*** → Quaternary ammonium compound^{+} (- N^{+} -)→ Highly ionized → Low lipid solubility → Not pass B.B.B. & distributed extracellularly

1- Acetylcholine (A.Ch.)

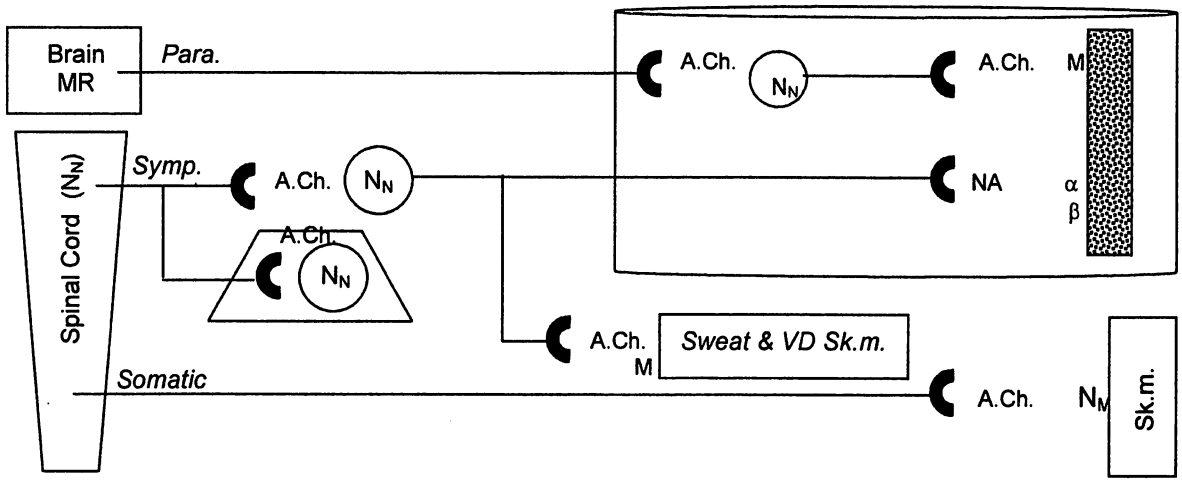
Natural Direct parasympathomimetic choline ester. It is the chemical transmitter at:

1- All post-ganglionic parasympathetic
2- Post-ganglionic sympathetic to thermo-regulatory sweat glands and V.D. fibers of Sk.m.
- Muscarinic
- Blocked by Atropine

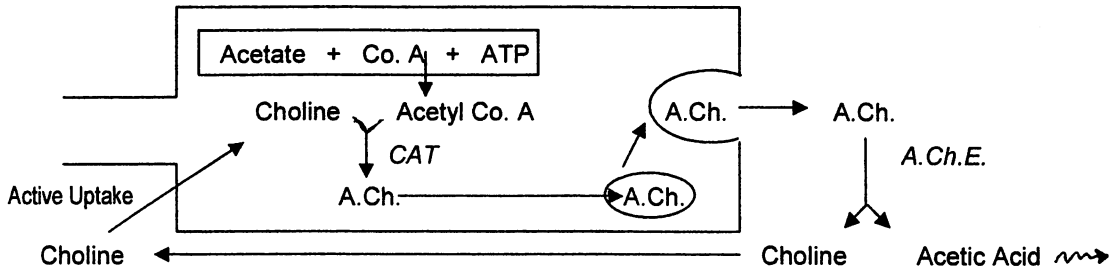
3- All autonomic ganglia (Symp. & Para.)
4- Adrenal medulla
- Nicotinic-Nerve (N_N)
- Blocked by Ganglion Blockers

5- Neuro-Muscular Junction
Motor End Plate of Sk.m.
- Nicotinic-Muscle (N_M)
- Blocked by N-M blocker e.g. Curare

6-C.N.S.: Brain (M mainly e.g. Basal ganglia) & Spinal cord (N_N mainly e.g. Renshaw Cells)



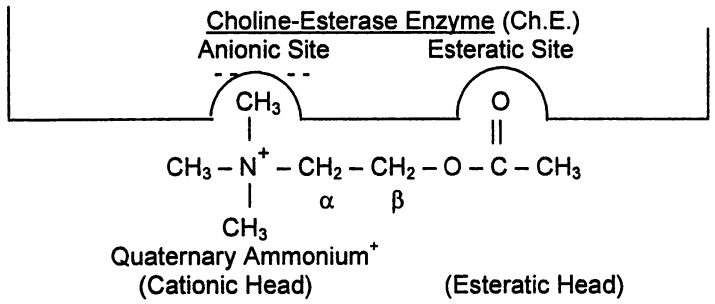
* Cholinergic Transmission:



1- Active uptake of choline by cholinergic nerve ending.
*This step is Rate limiting & can be inhibited by **Hemicholinium***
2- In Mitochondria: Acetate + Co. A + ATP → ADP + Acetyl Co. A → Cytoplasm
3- In Cytoplasm: Choline + Acetyl Co.A $\xrightarrow{\text{Choline Acetyl Transferase (CAT)}}$ A.Ch.
Triethylcholine inhibit utilization of choline by CAT.
NB) Hemicholinium & Triethylcholine → Inhibit the synthesis of A.Ch.
4- Storage of A.Ch. into membrane bound vesicles (*Blocked by **Vesamicol***).
5- Arrival of N.A. P. → Influx of Ca^{2+} → Release of A.Ch. by *Exocytosis*
*Release of A.Ch. can be inhibited by: **Mg^{2+}, Botulinum toxins & Procaine***
6- Fate of Released A.Ch. → Hydrolysis by A.Ch.E. → Recycling of Choline.

*Pharmacokinetics of A.Ch.:

1- Choline is a quaternary ammonium$^+$ - $\overset{|}{\underset{|}{N^+}}$ - → Low lipid solubility
2- Not absorbed orally, Do not pass BBB, Distributed Extracellularly
3- Metabolized by Choline esterase enzymes. A.Ch. attaches at BOTH sites of the enzyme → Immediate hydrolysis & release of choline → The enzyme remains acetylated for 150 milliseconds then regenerated.



NB) Types of Choline esterase Enzymes:

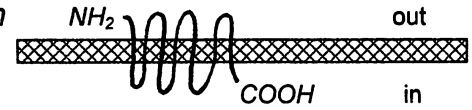
	Acetyl-Choline Esterase (A.Ch.E.) = True-Ch.E.	*Butyryl-Choline Esterase (B.Ch.E.) = Pseudo-Ch.E.*
1- Sites:	All cholinergic sites + CNS + RBCs	Liver & Plasma
2- Substrates:	- Endogenous A.Ch. - Methacholine *(Parasympathomimetic)*	- Exogenous A.Ch. - Butyrylcholine - Succinylcholine *(N-M blocker)* - Procaine *(Local anesthetic)* - Propanidid *(I.V. general anesthesia)*
3- Regeneration time	- 3 – 6 Months	- 2 -3 Weeks

* Mechanism of Ac`tion of A.Ch.:

A.Ch. Stimulates *Directly* Muscarinic & Nicotinic cholinergic receptors.

A) *Muscarinic (Peripheral Cholinergic) Receptors (MR or PCR):*

- *Membrane bound receptors linked to G-protein (Similar to Adrenoceptors).*
- *They are 5 types ($M_1 \rightarrow M_5$)*



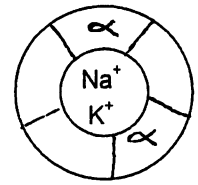
Receptor	Location	Mechanism	Blockers
M-1	Gastric parietal cells, autonomic ganglia, CNS & Pre-synaptic	↑ G_q → ↑ PLC → ↑ IP_3 & DAG	- Atropine - Pirenzepine
M-2	Smooth muscle, cardiac muscle, CNS & Pre-synaptic	- ↑ G_i → ↓ A.C. → ↓ cAMP - ↑ K^+ → Hyperpolarization - ↓ Ca^{2+}	- Atropine - Gallamine
M-3	Smooth muscle, Exocrine glands, Endothelium of B.V. & CNS	↑ G_q → ↑ PLC → ↑ IP_3 & DAG	- Atropine
M-4 & M-5	? CNS	?	?

B) *Nicotinic Receptors:*

- Ligand-Gated Ion (Na^+ & K^+) channel composed of α, β & γ subunits
- 2 A.Ch. must attach to 2 α subunits → Activation of ion channel → Depolarization

1- Nicotinic-Nerve (N_N):

a- Location: Autonomic ganglia, Adrenal medulla & CNS (Spinal cord Renshaw cells)
b- Agonists: A.Ch. & Nicotine S.D.
c- Antagonists: Ganglion blocker e.g. Nicotine L.D.



2- Nicotinic-Muscle (N_M):

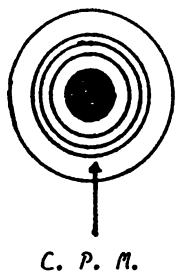
a- Location: Neuro-muscular junction at Motor end plate of Sk.m.
b- Agonists: A.Ch.
c- Antagonists: N-M blockers e.g. d-Tubocurarine (Curare)

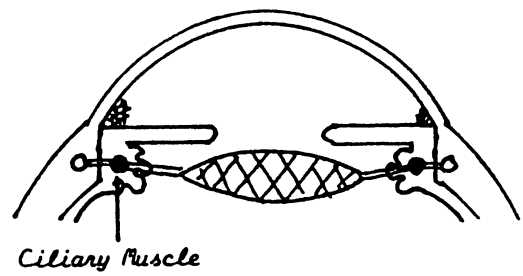
* Actions of A.Ch.:

A) Muscarinic Actions:

Miosis & Hypotension

1- Eye:





a- ↑ Constrictor pupillae muscle (CPM) → Miosis → Wide angle of filtration
b- ↑ Ciliary muscle → Open canal of Schlemm & Accommodation to Near vision
c- ↓ I.O.P. d- ↑ Lacrimation e- Conjunctival V.D.

2- C. V. S.:

a- ↓ S.A.N. → Bradycardia = -ve Chronotropic
b- ↓ A.V.N. → ↓ A-V conduction = -ve Dromotropic
} ↓ C.O.P.

c- ↑ Non-innervated M_3-receptors on endothelium → Release of Endothelium Derived Relaxing Factor (EDRF = Nitric oxide "NO") → ↑ soluble Ganylyl cyclase → ↑ cGMP → Dephosphorylation of Myosin Light Chain (MLC) → Relax smooth muscle of B.V. → V.D. → ↓ T.P.R.

d- Hypotension ↓ BOTH Systolic & Diastolic Bl.p. *(Reversed by Atropine)*

{NB: Endogenous A.Ch. affects mainly the heart (No para to B.V.) → ↓ C.O.P. mainly.
Exogenous direct Prasympathomimetics → Affect BOTH Heart & B.V. → ↓ BOTH COP & TPR)

3- Respiratory System → Bronchospasm & ↑ Secretions

4- G. I. T. → ↑ Secretions, ↑ Peristalsis & Relax sphincters

NB) Enteric Nervous System: A collection of neurons located in GIT wall → Myenteric (Auerbach's) & Submucosal (Meissner) plexues. They receives preganglionic para., postganglionic symp. & sensory nerves. Many transmitters e.g. A.Ch., NA, 5-HT, VIP, Sub. P. → Control motility & secretions. Can be considered as a 3rd division of A.N.S.

5- Urinary Bladder → Spasm of wall & relaxes sphincter

6- Uterus → Contraction of Non-pregnant uterus

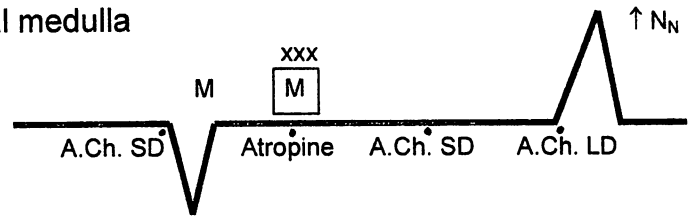
7- ↑ All exocrine glands including thermoregulatory sweating

B) Nicotinic Actions: Twitches & Hypertension

1- ↑ N_M → Skeletal muscle twitches
2- ↑ N_N → ↑ All ganglia & Adrenal medulla

NB) In Experimental:

1- A.Ch. S.D. → ↑ M only
2- A.Ch. in L.D. → ↑ M & ↑ N



3- A.Ch. L.D. after Atropine → ↑ Both Symp. Ganglia & Adrenal Medulla → Release of Both Adr. & NA → ↑ Both α + β → Hypertension (Reversal)
4- This Hypertension can be:
a- Reversed by α-Blocker
b- Abolished by Labetalol (α + β blocker) & Ganglion blockers

*** Therapeutic Uses of A.Ch.:** NOT used Clinically

1- Ineffective Orally 2- Short Duration 3- Non-Selective

* Synthetic Choline Esters:

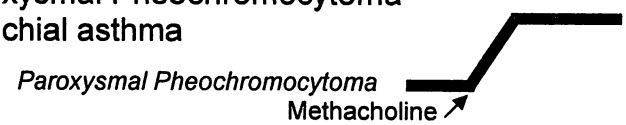
1- All are quaternary ammonium compounds – $\overset{\cdot}{\underset{\cdot}{N}}^{+}$- → Do Not pass BBB & Distributed extracellularly
2- Less metabolized → Effective Orally & Longer duration
3- When used Orally & S.C. → Selectivity
4- If injected I.M. or I.V. → Non-selective → Toxicity, Treat by Atropine
5- Contraindications:
   a- Thyrotoxicosis → Atrial fibrillation
   b- Angina pectoris: Hypotension → ↓ Coronary blood flow
   c- Bronchial asthma → Bronchospasm & ↑ Bronchial secretions
   d- Peptic ulcer → ↑ Gastric HCl

	A.Ch.	Methacholine	Carbachol	Bethanechol
1- Nature	- Natural	- Synthetic	- Synthetic	- Synthetic
2- Metabolism	- Both True & Pseudo	-True Only	- Not	- Not
3- Orally	- Not	- Irregular	- Complete	- Complete
		Oral > S.C.	Oral = S.C.	Oral = S.C.
4- Duration	- Very Short	- Longer	- Longer	- Longer
5- Muscarinic	+ + +	+ + +	+ + +	+ + +
6- Nicotinic	+ + +	±	+ + +	NO
7- Selectivity	- Not	- C.V.S.	- Eye, GIT & UB	- GIT & UB

* Therapeutic Uses of Synthetic Choline Esters:

1- Methacholine *(Acetyl-β-Methyl-Choline)*: *Oral dose > S.C. dose*

1- Treatment of Paroxysmal Atrial (Supraventricular) Tachycardia (PAT , PSVT)
2- Treatment of Peripheral Vascular Disease (PVD)
3- Provocative test to diagnose Paroxysmal Pheochromocytoma
4- Provocative test to diagnose Bronchial asthma



2- Carbachol *(Carbamoyl-Choline)*: *Oral dose = S.C. dose*

1- Eye drops to treat *Glaucoma* → Miosis + ↓ I.O.P. + Twitches (N_M)
2- Treatment of Non-obstructive e.g. Postoperative Paralytic ileus & gastric distention
3- Treatment of Non-obstructive e.g. Postoperative retention of urine

3- Bethanechol *(Carbamoyl-β-Methyl-Choline)*; *Oral = S.C.*

1- Treatment of Non-obstructive e.g. Postoperative Paralytic ileus & gastric distention
2- Treatment of Non-obstructive e.g. Postoperative retention of urine

NB) In Experimental:
1- A.Ch. & Carbachol → M + N →
*a-Their hypotension is **Reversed** by Atropine*
b- Eye drops → Miosis + Eye lid twitches
2- Bethanichol → M ONLY →
*a- Its hypotension is **Abolished** by Atropine*
b- Eye drops → Miosis ONLY without eye lid twitches

Cholinomimetic Alkaloids

- Direct Parasympathomimetics
- Not esters → Not metabolized by Ch.E. enzymes

Pilocarpine

Natural *Tertiary amine* (- N -) alkaloid of plant origin (Pilocarpus leaflet)

* Pharmacokinetics:

1- Absorbed orally
2- Distributed all over the body & passes B.B.B.
3- NOT metabolized by Ch.E., also does not ↓ Ch.E.
4- Excreted in urine

* Pharmacodynamics:

1- Direct stimulation of ***Muscarinic*** receptors mainly ± nicotinic
2- Selective on Eye & Exocrine secretions

* Therapeutic Uses:

1- Miotic eye drops → Miosis + ↓ I.O.P. + ↑ Lacrimation with**OUT** twitches
   a- Treatment of Glaucoma
   b- Counteract mydriatics after fundus examination
   c- Alternatively with mydriatics to cut recent adhesions between iris & lens
2- Sialagogue → ↑ Salivary secretion → Treat Xerostomia
3- Diaphoretic → ↑ Sweat secretion → Antipyretic in fever
4- Promote growth of hair *(Tonoscalpine Hair lotion)*

NB) **Muscarine**:

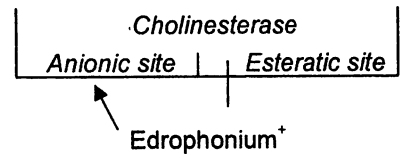
1- Alkaloid from toxic mushroom *(Amanita muscaria)* not natural in body
2- Selective ↑ Muscarinic receptors

Anti-Cholinesterases

- Indirect Parasympathomimetics → ↓ Ch.E. → Accumulation of endogenous A.Ch. → ↑ MR & NR → Endogenous A.Ch.-like actions.
- They are inactive in absence of endogenous A.Ch. e.g. denervated organs.
- They potentate drugs metabolized by Ch.E. e.g. A.Ch. *BUT NOT* carbachol.
- Endogenous A.Ch. & Anti-Ch.E. → ↓ Bl.p. by ↓ C.O.P. only. While Exogenous A.Ch. & other direct parasympathomimetics → ↓ Bl.p. by BOTH ↓ COP & ↓ TPR

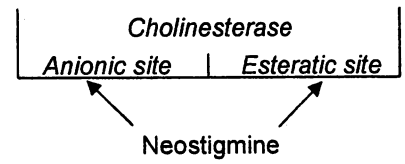
A) Reversible Anti-Ch.E.:

1- Quaternary ammonium Alcohol: (- N^+ -)



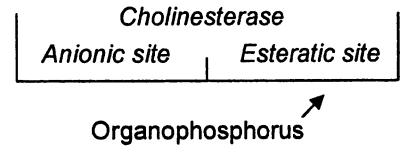
a- Edrophonium
b- Attaches to the *Anionic* site mainly
c- Not substrate → Not metabolized
d- Very short duration (5 minutes) = Rapidly reversible Anti-Ch.E.

2- Carbamate Derivatives (Esters):



a- Physostigmine, Neostigmine & Pyridostigmine
b- Esters → Attach at Both sites of the enzyme
c- Substrate for the enzyme → Hydrolysis
d- Enzyme remains carbamylated for ½ -6 hours minutes then regenerated

B) Irreversible Anti-Ch.E.:



1- Organophosphorus Compounds
2- Attach mainly to esteratic site at first reversibly then covalently = irreversibly → Aging of the enzyme
3- Their effect ends by resynthesis of new Ch.E. enzymes

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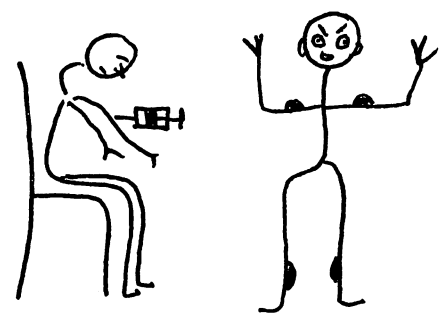
1- Edrophonium *(Tensilon)*



1- Synthetic quaternary ammonium alcohol (- N^+ -)
2- Rapidly reversible Anti-Ch.E. (5 minutes)
   a- Attaches mainly to the anionic site.
   b- Not substrate → Not metabolized by Ch.E.
4- Excreted unchanged in urine
5- More specific on skeletal muscle than Neostigmine
6- Uses: I.V. → Immediate onset & short duration (5 minutes)
   a- Diagnosis of ***Myasthenia gravis*** *(I.V. 2 mg if no improvement within 45 min inject 8 mg)*
   b- Treatment of ***Myasthenic crisis*** & to *differentiate* it from ***Cholinergic crisis***

Myasthenic crisis	Cholinergic crisis
1- Under treatment → ↓ A.Ch. → Paralysis 2- Improved by Edrophonium	1- Over treatment → ↑ A.Ch. → Depolarizing block 2- Worsened by Edrophonium

   c- Initiate treatment of Curare poisoning
   d- Paroxysmal Atrial (Supraventricular) Tachycardia "PAT or PSVT"

	Physostigmine *(Eserine)*	Neostigmine *(Prostigmine)*
1- Nature:	1-Natural Tertiary amine alkaloid (- N -) of plant origin (Calabar beans)	1- Synthetic Quaternary ammonium compound (- N^+ -)
2- Kinetics:	2-a- Absorbed Orally b- Passes B.B.B. c- Rapid metabolism by Ch.E. d- Short duration	2-a- Irregularly absorbed orally b- Do NOT pass B.B.B. c- Slowly metabolized by Ch.E. d- Longer duration of action
3- Dynamics:	3- Reversible Anti-Ch.E. → Endogenous A.Ch. Like → ↑ MR & ↑ NR	
4- Uses:	a- More specific on Eye → Miosis + ↓ IOP + Twitches b- C.N.S. Stimulation 4-a- Eye drops (½ - 1 %): - Treat glaucoma - Counteract mydriatics - Alternatively with mydriatics to cut recent adhesions between iris & lens b- I.V. in Atropine poisoning c- Tried in Alzheimer's disease	a- More specific on GIT & UB ↑ Wall & ↓ Sphincters b- Direct Sk.m. Stimulant effect 4-a- Myasthenia Gravis: - Diagnosis (1/2 – 1 mg IM) - Treatment (15 mg / 6 hours po) b- Curare poisoning (I.V.) *NB) In (a & b) add Atropine to block the unwanted muscarinic actions* c- Paralytic ileus (S.C. & I.M.) d- Retention of urine (S.C. & I.M.) e- P.A.T. (S.C. & I.M.)
5- Toxicity:	5-a- Exaggerated A.Ch. like actions b- CNS stimulation → Convulsion	5-a- Exaggerated A.Ch. like actions b- No convulsions
6- Management of Toxicity:	6-a- Atropine b- Anticonvulsants e.g. Diazepam	6- Atropine No need for anticonvulsants

* New Drugs in Treatment of Alzheimer's Disease:

More selective Central Anti-Ch.E. → ↑ Central A.Ch. in Hippocampus → Improve cognitive functions e.g. Memory, recognition & ability to speak.

1- **Tacrine** *(Cognex 10-40 mg po)*: May cause nausea, vomiting & hepatotoxicity

2- **Donepezil** *(Aricept 5 - 10 mg po od)*: More selective & less hepatotoxicity

3- **Rivastigmine** *(Exelon 1.5 – 6 mg po bid)*

* Neostigmine Substitutes:

1- **Demecarium** *(Humorsol)*: Eye drops in Glaucoma

2- **Benzpyrinium** *(Stigmonene)*: Useful in Paralytic ileus & Retention of Urine

3- **Pyridostigmine** *(Mestinon)* } - Like neostigmine. Reversible Anti-Ch.E.

4- **Distigmine** *(Adcostigmine)* } - More specific on Sk.m. → NO need to add Atropine

5- **Ambenonium** *(Mytelase)* } - Treatment of Myasthenia Gravis

Myasthenia Gravis

A) Etiology :

- An autoimmune disease. Antibody formation against N_m-receptors of motor end plate.

B) Diagnosis :

1- ***IV Edrophonium*** : 2 mg if no improvement within 45 seconds, inject 8 mg.
Also useful to asses therapy & to differentiate between Cholinergic & Myasthenic crises.
2- IM Neostigmine 0.5 mg + Atropine 0.5 mg.
3- Auto-antibody titer.

C) Treatment :

1- ***Neostigmine*** (15 mg/6 hours) is the standard drug.
Also Pyridostigmine & Ambenonium → More selective on Sk.m. → No need for Atropine
2- Atropine may be added to block the unwanted muscarinic actions of Neostigmine = Corrective.
3- Ephedrine & Caffeine are adjuvant to Neostigmine.
4- Immuno-suppressants : Steroids e.g. Prednisolone & Antimetabolites e.g. Azathioprine.
5- Thymectomy. 6- Plasma-phoresis.

D) Drugs Contraindicated in Myasthenia Gravis :

1- Skeletal muscle relaxants.
2- Antimicrobials : Aminoglycosides e.g. Streptomycine.
3- Antiarrhythmics : Quinidine, lidocaine & phenytoin.
4- β-Blockers e.g. Propranolol. 5- Lithium. 6- d-Penicillamine.

Irreversible Anti.Ch.E.
Organophosphorus Compounds

1- **Insecticides**: *Parathion* & *Malathion* → In insect & man → Toxic Paraoxon & Malaoxon. Malathion is less toxic to man.

2- **War Gases**: Sarin, Tabun & Soman.

3- **Metrifonate** *(Bilarcil)*: Oral Anti-Schistosoma hematobium

4- **Isoflurophate** (Di-isopropyl-Fluro-Phosphate = DFP): Eye ointment in glaucoma

5- **Echothiophate** *(Phospholine)*: Eye drops in Glaucoma

* Pharmacokinetics:

1- Most of then have high lipid solubility	*Except* Echothiophate
2- Absorbed from all sites even intact skin	*Except* Echothiophate
3- Distributed all over the body & pass B.B.B.	*Except* Echothiophate
4- Long duration of actions	**Especially** Echothiophate

* Pharmacodynamics of Organophosphorus Compounds:

1- Irreversible Anti-Ch.E.:
   a- They phosphorylate the esteratic site of the enzyme
   b- At first reversibly → then Covalently & Irreversible → Aging of the enzyme
2- Accumulation of endogenous A.Ch. → ↑ MR & NR
3- Their effect ends by resynthesis of new Ch.E. (3 week for B.Ch.E. and up to 3 months for A.Ch.E.)

* Organophosphorus Poisoning:

I- Chronic Toxicity → Neuropathy

II- Acute Toxicity:

A) Causes of Acute Toxicity:
1- Occupational: Agricultural insecticides
2- Domestic: Children & Contamination of food
3- Intentionally to commit suicide or homicide

B) Manifestations of Acute poisoning:
1- Muscarinic: Miosis, Lacrimation, Salivation, Bradycardia, Hypotension, Bronchospasm & ↑ secretions, colic, diarrhea & urination
2- Nicotinic: Sk.m. twitches followed by paralysis due to prolonged depolarization
3- C.N.S.: Convulsions followed by coma

C) Cause of Death: respiratory failure (Central & Peripheral)

D) Management of Acute organophosphorus Poisoning:
1- Care of Respiration: Endotracheal intubation + Artificial respiration + Aspiration
2- Decontamination:
   a- Oral poisoning → Stomach wash by $NaHCO_3$
   b- Contamination of skin: Remove contaminated clothes + skin wash
3- **ATROPINE** → Life saving:
   a- 1 -2 mg I.V. or I.M. / 5 – 10 minutes till → Mydriasis, Dry mouth & tachycardia. Keep the patient Atropinized for at least 48 hours
   b- Atropine blocks C.N.S. & Peripheral Muscarinic receptors
4- **Choline-esterase Reactivators = Oximes**:
   a- Preparations:
      - Pralidoxime *(PAM, Protopam)*: Do Not pass B.B.B.
      - Di-Acetyl-Monoxime *(DAM)*: Passes B.B.B.
      - Obidozime: Passes B.B.B.
   b- Effective *ONLY* in organophosphorus poisoning
   c- More effective in early poisoning *before* aging of the enzyme
   d- React with organophosphorus → Harmless & easily excreted compounds = **Chelation**
   e- Regenerate recently inhibited enzymes (before aging) & prevent further inhibition
5- Anti-convulsants e.g. Diazepam or $MgSO_4$.
6- Fresh blood transfusion or exchange may be needed.

Parasympathomimetics
Cholinomimetics , Muscarinic Agonists

These are drugs that stimulate muscarinic receptors either directly or indirectly

A) Direct Parasympathomimetics:

They stimulate directly the muscarinic receptors:

1- Cholinesters:

a- Natural: A.Ch. b- Synthetic: Methacholine, Carbachol & Bethanichol

2- Alkaloids: Pilocarpine & Muscarine

B) Indirect Parasympathomimetics = Anti-Cholinesterases:

They ↓ Ch.E. → Accumulation of Endogenous A.Ch. → ↑ MR & ↑ NR → Endogenous A.Ch.-like actions. They depend on the presence of endogenous A.Ch.

1- Reversible:

a- Quaternary ammonium alcohol: Edrophonium

b- Carbamate derivatives (Esters): Physostigmine & Neostigmine

2- Irreversible: Organophosphorus compounds e.g. Echothiophate

NB) Cholinoceptor Antagonists = A.Ch. Antagonists

1- Muscarinic Receptor Antagonists; ***Parasympatholytics*** e.g. Atropine

2- Nicotinic Receptor Antagonists:

a- N_N-Blockers: ***Ganglion blockers*** e.g. Trimethaphan

b- N_M-Blockers: ***N-M blockers*** e.g. d-Tubocurarine

Parasympatholytics
Anti-Muscarinic , Anti-Cholinergic

These are drugs that compete with A.Ch. for the muscarinic receptors

* *Classification According to Selectivity:*

1- Non-Selective: Atropine → Blocks *ALL* M-receptors ($M_1 - M_5$)

2- Selective:

a- Selective M_1-blocker: Pirenzepine

b- Selective M_2-blocker: Gallamine

* *Classification According To Nature:*

1- Natural Alkaloids: Atropine & Hyoscine (Scopolamine) → Plant origin e.g.

a- Atropa belladonna b- Datura stramonium c- Hyoscyamus niger

2- Synthetic Atropine Substitutes:

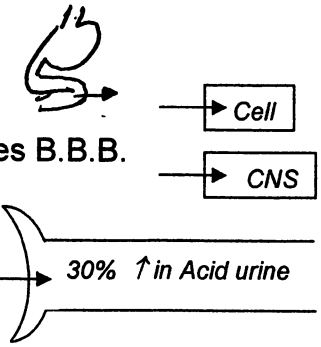
a- Mydriatics b- Antisecretory antispasmodics

c- Anti-Asthmatics d- For Urinary incontinence e- For Parkinsonism

Atropine

- Natural parasympatholytic tertiary amine alkaloid of plant origin (- N -)
- Ester of Tropic acid + Tropine base

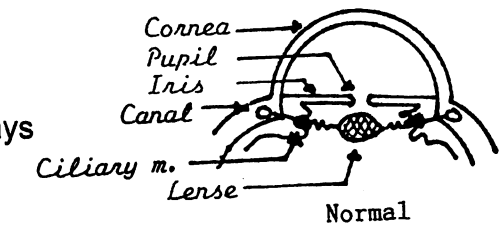
*Pharmacokinetics:



1- Well absorbed orally, mucous membranes & parenterally
2- Distributed all over the body (intra & extra-cellularly) & passes B.B.B.
3- Partially metabolized in liver (70%)
4- Excreted in urine partially unchanged (30%)
Acidification of urine → ↑ Its urinary excretion

* Pharmacodynamics:

A) Local Actions:

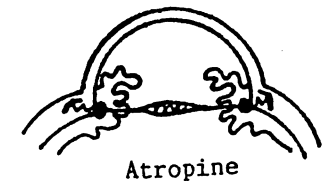


1-Eye:

a- Eye Drops 1%, Onset 60 minutes, Duration 7-10 days
b- Paralysis of C.P.M. → Passive Mydriasis
- Loss of Light reflex
- Narrow Angle of Filtration & Spaces of Fontana

c- Paralysis of Ciliary muscle → Cycloplegia
- Loss of Accommodation to near vision
- Close Canal of Schlemm

d- ↑ I.O.P.
e- ↓ Lacrimation



2- Skin & mucous membranes → Local Anodyne (Analgesic) action

B) Systemic Parasympatholytic Actions:

Atropine blocks ALL types of muscarinic receptors ($M_1 \rightarrow M_5$)

1- Eye:

a- Single oral or parenteral dose → No mydriasis
b- Doubled dose → Mydriasis for 6 – 8 hours

2- C.V.S.:

a- Heart:

1- Tachycardia:
- Affects mainly resting heart rate due to predominance of vagal tone
- Does not affect maximal heart rate due to exercise
- Initial bradycardia may occur due to either:
  Initial stimulation of C.I.C. in C.N.S.
  Initial block of presynapticM_1-receptors → ↑ Release of A.Ch.

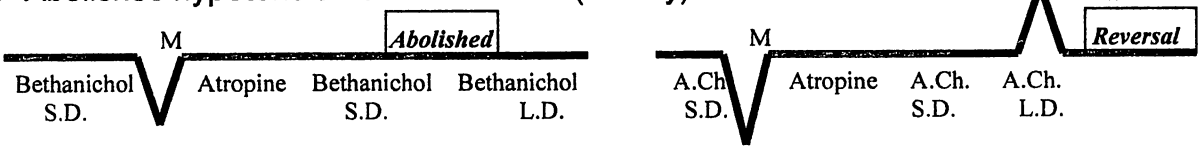
2- ↑ A-V conduction

6- Blood vessels:

1- Small therapeutic dose → Minimal effect (No parasympathetic tone on B.V.)
2- Large dose especially in children → Atropine Flush of face & chest

c- Blood pressure:

1- Small therapeutic dose → Minimal effect
2- Reverses hypotension of A.Ch. & Carbachol (M + N)
3- Abolishes hypotension of Bethanichol (M only)



3- Respiratory Tract:

a- Bronchodilatation
b- Dry bronchial secretions & ↓ Mucocilary clearance → Not suitable in B.A.
NB) ***Ipratropium & Tiotropium*** are atropine substitutes → Bronchodilatation with less effect on bronchial secretion. Used by inhalation in B.A. & C.O.P.D.

4- G. I. T.:

a- ↓ Salivary secretion → Dry mouth = Xerostomia
b- ↓ Gastric HCl (***Pirenzepine & Telenzepine*** are more selective M_1-blockers)
c- Relax wall → Antispasmodic (***Propantheline*** is more selective)
d- Spasm of sphincters → Constipation

5- Urinary Bladder:

a- Relax Ureter & Detrusor muscle } - Retention of urine
b- Spasm of sphincters & Trigone } - ***Emepronium & Oxybutynin*** → more selective

6- Skin: ↓ Sweat → Anhidrosis → Dry, red & hot skin

7- ↓ ALL secretions Except milk, bile & urine

C) C.N.S. Actions of Atropine:

1- Mainly *C.N.S. Stimulant* → Restlessness, excitation, hallucination & mania
(Central Anticholinergic syndrome, Toxic Psychosis)

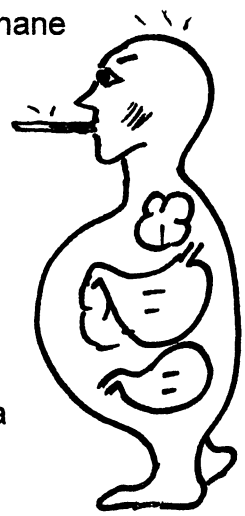
2- Medulla: - ↑ R.C. (Analeptic) - ↑ C.I.C. (Explains initial bradycardia)
- ↓ Vomiting center (Anti-emetic)

3- ↓ Basal Ganglia → Anti-Parkinsonian (***Benztropine*** is more selective)

*Therapeutic Uses of Atropine:

Dose: 0.3 – 0.6 mg Orally & Parenterally

1- Antidote for Parasympathomimetic poisoning e.g. Oragophosphorus
2- Mydriatic in Iridocyclitis, Uveietis & Corneal ulcer
3- Vagotonia & Vaso-vagal attacks = Carotid sinus syndrome
4- Heart block due to β-Blockers, Digitalis & Myocardial infarction
5- Bronchial asthma (***Ipratropium & Tiotropium***)
6- Peptic ulcer (***Pirenzepine & Telenzepine***)
7- Colic e.g. Intestinal, Biliary & Renal. Also antagonizes spasmogenic effect of Morphine (***Propantheline***)
8- Diarrhea
9- Nocturnal enuresis & Urinary incontinence (***Emepronium & Oxybutynin***)
10- Hyperhidrosis
11- Preanesthetic medication (***Hyoscine***):
   a- ↑ R.C. → Prevent respiratory depressant effect of Anesthesia & Morphine
   b- ↓ Salivary & Bronchial secretion → Prevent Aspiration pneumonia
   c- Protect the heart form the depressant effect anesthesia e.g. Halothane
12- Vomiting & Motion sickness (***Hyoscine***)
13- Parkinsonism (***Benztropine***)



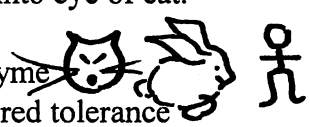
* Adverse Effects & Toxicity of Atropine:

A) Manifestations:

1- Toxic psychosis → Hallucination, mania → convulsions → Coma
2- Parasympatholytic manifestations:
   a- Mydriasis, photophobia, blurring of vision & glaucoma
   b- Dry, red & hot skin c- Dry mouth d- Tachycardia
   e- Distention, constipation & retention of urine
3- Allergy

N.B.)

1- Toxicity can occur even after instillation of Atropine eye drops into a child → Naso-lacrimal duct → Naso-pharynx → G.I.T. → Absorption → Systemic effect.
   In children either use Atropine ointment or press on inner canthus after putting the drops
2- Confirm atropine poisoning by putting a drop of patient's urine into eye of cat.
3- Cat → Natural supersensitivity
   Rabbit → Natural Tolerance. It has excess atropine esterase enzyme
   Human → At first normal response then after long use → Acquired tolerance



B) Management of Atropine Poisoning:

1- Physostigmine (I.M. or I.V.) to correct peripheral & central manifestations
2- If psychosis → Diazepam
3- If Hyperthermia → Ice bags & cold bathes
4- If oral poisoning → Stomach wash
5- If respiratory failure →Artificial respiration.

* *Contraindications of Atropine*:

1- Fever
***2- Glaucoma
3- Bronchial asthma
4- Tachycardia
5- Constipation & paralytic ileus
***6- Enlarged prostate (Benign Prostatic Hyperplasia)
7- After neostigmine in curare poisoning → Severe initial bradycardia
8- Allergy to Atropine

Hyoscine (Scopolamine)

- Natural Parasympatholytic tertiary amine alkaloid of plant origin
- It is an ester between tropic acid and scopine base
- Pharmacology similar to atropine *BUT*:

1- Shorter duration of action
2- No local anodyne action
3- Parasympatholytic actions are *Stronger* on Eye & Secretions
But Weaker on G.I.T. & Heart → No tachycardia
4- **C.N.S.**:
a- Mainly *Depressant* → Sedation & Hypnosis (Dreamless sleep, ↓ R.E.M.)
But if used alone in presence of pain → Hyperalgesia, Excitation & Delirium
b- Amnesia to recent events
c- Euphoria
d- ↓ Vomiting center → Anti-Motion sickness
e- ↓ Basal ganglia → Anti-Parkinsonian
f- ↑ R.C., ↑ C.I.C.
g- Large dose → Excitation → Central anticholinergic syndrome

* *Therapeutic Uses of Hyoscine*:

Dose: 0.3 - 0.6 mg Orally, parenterally & Transdermal patch

1- Preanesthetic medication → Better than Atropine
a- C.N.S. Depressant → Sedation, Hypnosis & amnesia → ↓ Dose of Anesthesia
b- More ↑ R.C. & More Antisecretory
c- No tachycardia → Safer in Thyrotoxic patients

2- Prophylaxis of Motion sickness (Air sickness)
3- Meniere's disease & Labrynthitis
4- Parkinsonism

Synthetic Atropine Substitutes

A) Mydriatic Atropine Substitutes:

All are contraindicated in Glaucoma

	Atropine	Homatropine	Cyclopentolate & Tropicamide	Eucatropine
1- Concentration	1%	1 - 2 %	0.5 – 1 %	2 – 5 %
2- Onset	60 minutes	60 Minutes	30 Minutes	20–30 Min
3- Duration	7-10 days	24 Hours	6 Hours	3 – 4 Hours
4- Cycloplegia	+ + +	+ + +	+ +	NO
5- # by Eserine	Partial	Complete	Complete	Complete
6- Uses	Iritis & Corneal ulcer	Fundus Examination		

Comparison between ocular effects of Atropine & Ephedrine

	Atropine	Ephedrine
1- Mechanism	Block M.R. in C.P.M. & C.M.	↑ α_1 in D.P.M. & B.V.
2- Onset	60 minutes	Faster
3- Duration	7 – 10 days	Shorter
4- Size of pupil	Passive Mydriasis	Active Mydriasis
5- Light reflex	- ve (Absent)	+ve (Intact)
6- Ciliary muscle	Cycloplegia	No cycloplegia
7- Near vision	No accommodation	Preserved
8- I.O.P.	↑ I.O.P.	↓ I.O.P.
9- Conjunctival B.V.	Normal	V.C. → Decongestion

B) Antisecretory Antispasmodic Atropine Substitutes

1- Hyoscine Butyl Bromide *(Buscopan)* : 20 mg Orally, Rectal, I.M. & I.V.

2- Oxphenonium *(Spasmodin)*: 5 mg orally } -Quaternary ammonium compounds

3- Propantheline *(Pro-Banthine)*: 15 mg Orally } - Minimal absorption from G.I.T.

*** Pharmacological Actions & Therapeutic Uses:**

1- Small dose → Parasympatholytic Selective on G.I.T.
   a- Antisecretory → Treat Peptic ulcer
   b- Anti-Spasmodic → Treat colic e.g. Intestinal, Biliary & Renal
2- Large dose → Ganglion block & N-M block

NB)

- **Pirenzepine** *(Gastrozepine)*: 25 mg ½ hour before meal
- **Telenzepine**

1- Selective M_1-blockers → ↓ Gastric acidity → Treat Peptic ulcer
2- Almost No C.N.S., Blurring of vision, Dry mouth or Tachycardia

C) Atropine Substitutes in Urinary Incontinence

- **Emepronium** *(Cetiprine)*: 100 mg Orally at bed time
- **Oxybutynin** *(Uripan, Ditropan)*: 5 mg tds

1- ↓ Motility of urinary bladder & Spasm of sphincters
2- Useful in Nocturnal enuresis, Urinary incontinence & to prevent bladder spasm after uro-surgery

D) Bronchodilator Atropine Substitutes

- Ipratropium *(Atrovent)*; Inhalation 80 ug 3-4 times/day → Prophylaxis of B.A.
- Oxytropium bromide: Derivative of **Hyoscine**. Similar to Ipratropium.
- Tiotropium *(Spiriva)*: Inhalation 18 ug od in C.O.P.D.

1- They produce bronchodilatation without dryness of bronchial secretions
2- The are quaternary ammonium compounds → Limited absorption from bronchi → Limited systemic adverse effects

E) Anti-Parkinsonian Atropine Substitutes

1- **Benztropine** *(Cogentin)*: } - Tertiary amines → Pass B.B.B.
2- **Benzhexol = Trihexyphenidyl** *(Artane)*: } - ↓ Rigidity & ↓ Tremors

Autonomic Ganglia

- Both symp. & para. Ganglia contain ***Nicotinic*** (N_N, N_G) cholinoceptors mainly.
- Drugs may be Ganglion stimulants (↑ N_N) or Ganglion blockers (↓ N_N).

Ganglion Stimulants

1- They stimulate $N_{N,G}$-receptors of *BOTH* sympathetic & parasympathetic ganglia

2- They have limited therapeutic use.
Actually, ***Nicotine*** (Tobacco) represents medico-socio-economic problem

3- Nicotine S.D. → Depolarization → Repolarization = Ganglion stimulant
Nicotine L.D. → Initial depolarization = Initial stimulation → Prolonged depolarization = Depolarizing block (Non-competitive Partial agonist or Dualist)

4- They include:
a- **Nicotine S.D.**
b- **Lobeline S.D.**
c- Tetra-Methyl-Ammonium (T.M.A.)
d- Di-Methyl-Phenyl- Piperazinium (DMPP)
e- A.Ch. (M + N)
f- Carbachol (M + N)

Nicotine

Natural tertiary amine alkaloid of plant origin (Tobacco leaves).

* *Pharmacokinetics:*

1- Absorption from ALL sites including the intact skin.
2- Distribution: ALL over the body and passes B.B.B. & Placental Barrier
3- Metabolized in Liver & Lung
4- Excreted in urine & Milk.

* *Pharmacodynamics:*

A) C. N. S.: STIMULATION

1- Anxiety → Hyper-reflexia → Tremors → Convulsions → Coma → Death.
2- ↑ R.C. 3- ↑ V.M.C. 4- ↑ C.T.Z. 5- ↑ A.D.H. → Anti-diuretic.

B) Stimulation of Autonomic Ganglia & Adrenal Medulla;

1- C.V.S.: Sympathetic (↑ Ganglia, ↑ Adrenal Medulla & ↑ V.M.C.)

a- ↑ Heart → + ve Ino, +ve Chrono & +ve Dromo → ↑ C.O.P.
b- ↑ Cardiac Work & Oxygen consumption → May cause Angina pectoris.
c- ↑ Excitability & Automaticity → May cause Cardiac Arrhythmia.
d- V.C. → ↑ T.P.R. → Hypertension & P.V.D. (Buerger's disease).

2- G. I. T.: Parasympathetic

a- ↑ Secretions e.g. Salivation & Gastric acidity → May cause Peptic ulcer.
b- ↑ Motility c- ↑ C.T.Z. → Nausea d- ↓ Appetite

C) ***Acquired Tolerance*** on prolonged use & ***Cross Tolerance*** with Lobeline.

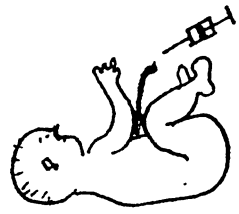
* *Adverse Effects of Chronic Tobacco Smoking:*

1- C.N.S. → Anxiety & tremors.
2- Eye → Spasm of retinal vessels → ↓ Visual acuity → Tobacco Amblyopia
3- Respiration → Irritation → Smokers cough & Cancer (Lip, tongue, larynx & lung)
4- C.V.S. → Angina, Arrhythmia, Hypertension & P.V.D. (Buerger's disease)
5- Blood → ↑ F.F.A. & Platelet stickiness → Atherosclerosis
6- G.I.T. → ↑ Salivation, Nausea & Peptic ulcer.
7- Liver → H.M.E. induction → ↑ Metabolism of Theophylline
8- Pregnancy → Abortion, premature labor, small baby & Teratogenicity.

* *Contraindications of Smoking:*

1- C.V.S.: Angina, arrhythmia, hypertension & P.V.D.
2- Respiration: Cough & Bronchial asthma
3- G.I.T.: Peptic ulcer
4- Pregnancy (Avoid active as well as passive smoking)

N.B.) Lobeline



1- Similar to Nicotine BUT WEAKER.
2- ↑ Chemo-receptors → Reflex ↑ R.C. → ***Reflex Analeptic***.
3- WAS use Intra-umbilical in Neonatal Asphyxia.

Ganglion Blockers

A) Depolarizing Ganglion Blockers:

1- Examples: ***Nicotine*** Large dose & ***Lobeline*** large dose.
2- Initial Depolarization **(Stimulation)** → Maintained Depolarization **(Block)** → Dualist or Partial Agonist. Reversible Non-competitive block. Block ends by metabolism of G.B.
3- Not used Clinically → Initial stimulation of ganglia & Very toxic.

B) Competitive Ganglion Blockers:

1- They ***Compete*** with A.Ch. for N_G receptors of autonomic ganglia.
2- They are ***Antagonists*** → Affinity + No Efficacy + Slow dissociation.
3- They block ***Both*** Parasympathetic & Sympathetic ganglia.
4- Effects are due to block of dominant ganglia:
NB) Isolated organs contain Parasympathetic ganglia ONLY.

Site	Dominant ganglia	Effect of Ganglion Blockers
1- Eye	Para.	Passive Mydriasis + Cycloplegia + ↑ I.O.P.
2- Heart	Para.	Tachycardia
3- Bronchi	Para.	Bronchodilatation + Dry bronchial secretions
4- G.I.T.	Para.	Xerostomia, ↓ All secretions, Relax wall & Spasm of sphincters → Distention & Constipation
5- U.B.	Para.	Relax wall & spasm of Sphincters → Retention of Urine
6- Erection	Para.	Impotence
7- Ejaculation	Symp.	Failure of ejaculation
8- B.V.	Symp.	- Arterial V.D. → ↓ T.P.R. → ↓ After load - Venous V.D. → ↓ V.R. → ↓ E.D.V. → ↓ Preload & ↓ C.O.P. - Hypotension
9- Sweat	Symp.	Dry skin (Anhidrosis)

NB) Competitive Ganglion blockers are NOT commonly used clinically due to many side effects → Mainly ↓ Para. → Atropine like effects.

NB) Correction of Adverse Effects of Ganglion blockers:
1- Parasympathomimetic e.g. Neostigmine.
2- Sympathomimetic e.g. Ephedrine.

Classification of Ganglion Blockers:

A) Quaternary Ammonium Compounds: → $-\overset{\overset{|}{}}{\underset{|}{N^+}}-$ → No BBB & Extracellular
1- *Tetra-Ethyl-Ammonium* (TEA) 2- *Pentolinium* 3- *Pentamethonium* (C-5)
4- *Hexamethonium* (c-6) 5- *Chlorisondamine* (Ecolid)
B) Tertiary Amines: *Pempidine* → Pass BBB, All over the body ($R-\overset{\overset{R}{|}}{N}-R$)
C) Secondary Amine : *Mecamylamine* → BBB, All over the body ($R-\overset{\overset{H}{|}}{N}-R$)
D) Mono-Sulfonium: *Trimethaphan* (Arfonad) I.V. Infusion
1- Not Orally, Not B.B.B., Extracellular & Not hepatic metabolism
2- Hypotension: Ganglion Blocker + Histamine Release + Direct V.D.
3- I.V. Infusion in → Controlled hypotension during plastic & neurosurgery
→ Emergency hypertension (Encephalopathy)
4- Toxicity → Hypotension + Intravascular thrombosis + Renal Failure

Pharmacology Of The Eye

* Autonomic Supply of the Eye:

1- ***Parasympathetic*** → Cranial Nerves:

a- III (Occulomotor):

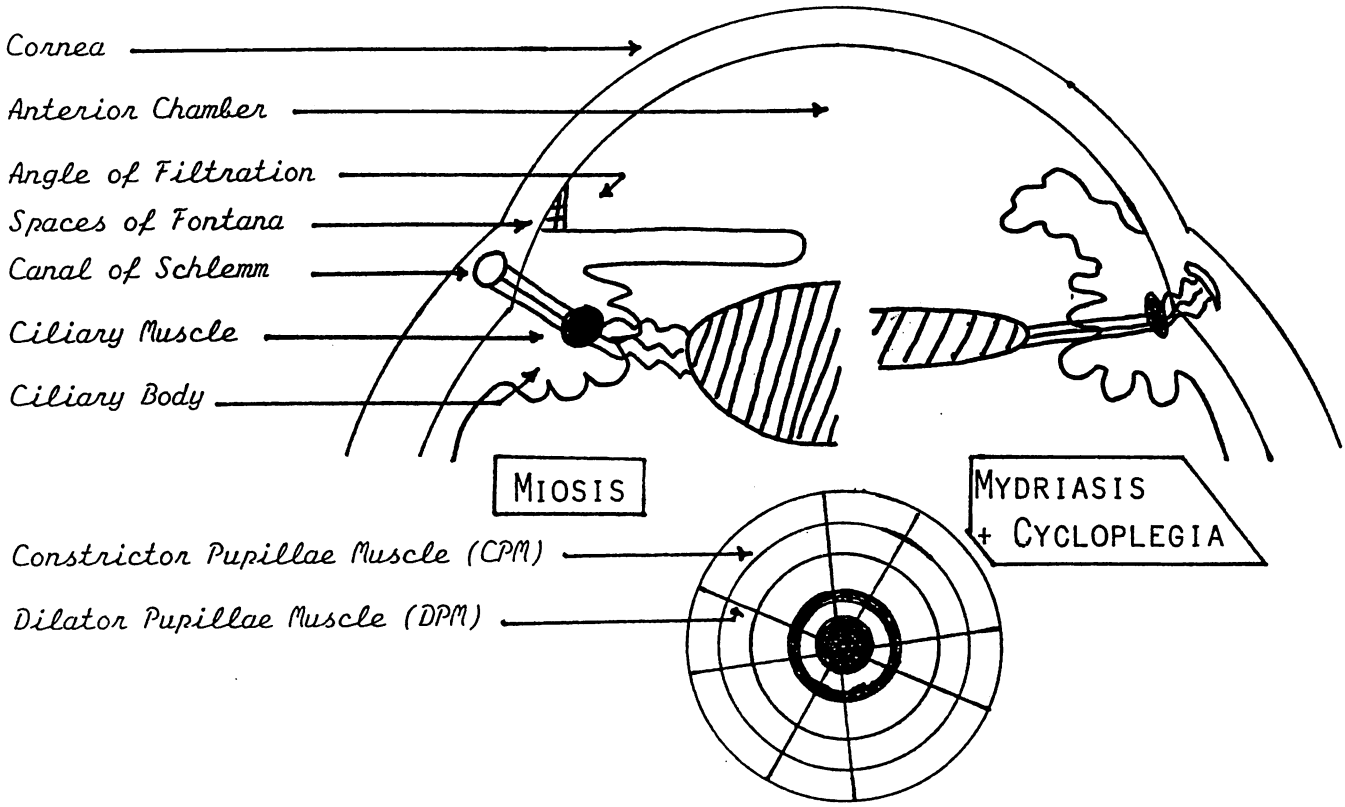
- Constrictor Pupillae Muscle (CPM) → Miosis → Light Reflex.
  → Wide Angle of Filtration & Spaces of Fontana
- Ciliary Muscle (CM) → Accommodation to near vision & Open canal of Schlemm.

b- V (Trigeminal): Sensations from cornea and conjunctiva. } Corneal & Conjunctival
c- VII (Facial): Lachrymal glands and Orbicularis oculi muscle. } Reflexes

2- ***Sympathetic***:

a- Dilator Pupillae Muscle (DPM) → α_1 → Active Mydriasis.
b- Ciliary body:
- α_2 → ↓ cA.M.P. → ↓ Aqueous humour formation.
- β → ↑ c.AM.P. → ↑Aqueous humour formation.

c- Blood vessels (α_1) → V.C.
d- Levator palpebrae superiosis → Retraction of upper eye lid.
c- Retrobulbar (Muller's) muscle → Exophthalmos.



Drugs Affecting The Size Of Pupil

I- Miotics

(↑ Parasympathetic or ↓ Sympathetic)

A) Parasympathomimetics:

1- ***All*** ↑ M.R. in:
   a- C.P.M. → Miosis → Wide Angle of Filtration & Spaces of Fontana } ↓ **I.O.P.**
   b- Ciliary muscle → Spasm → Open canal of Schlemm } ↓ **I.O.P.**
   → Accomodation to near vision
   c- ↑ Lacrimation & Conjunctival V.D.
2- ***Some*** → ↑ N_M → Upper eye lid Twitches (***NOT*** with Bethanichol or Pilocarpine)
3- **Examples**:
   a- Direct parasympathomimetics:
      - Choline esters: Bethanichol (M only) & Charbachol 0.75-3% (M & N)
      - Alkaloids: Pilocarpine 1-2% (M only)
   b- Indirect Parasympathomimetics = Anti-Ch.E. → All A.Ch. like → M & N
      - Reversible: Physostigmine (0.25-1%) & Demecarium (0.125-0.5%)
      - Irreversible = Organophosphorus → Echothiophate (0.03-0.25 %)
4- **Therapeutic Uses**:
   a- Glaucoma
   b- Counteract Mydriatics
   c- Alternatively with mydriatics to cut recent adhesions between iris & lens

B) Morphine → Systemic Effect

1- **Morphine** → C.N.S. → ↑ Opiate Receptors of III C.N. Nucleus (Edinger Westphal ganglia) → Oculomotor Nerve → Ciliary Ganglia (N_N) → Eye → A.Ch. → ↑ M.R. of C.P.M. → Severe Miosis (Pin Point Pupil)
2- **P.P.P. of Morphine can antagonized by**:
   a- Systemic Naloxone → Block Opiate receptors in C.N.S.
   b- Systemic Ganglion Blockers → Block Ciliary Ganglia
   c- Topical Atropine → Block M-receptors on C.P.M.

C) Guanethidine:

1- ↓ **Release** of Noradrenaline →
   a- Paralysis of D.P.M. → Passive Miosis → ↓ IOP.
   b- ↓ Levator palpebrae superiosis & ↓ Muller's muscle → ↓ Exophthalmos.
2- **Therapeutic uses** → Eye Drops in:
   a- Glaucoma either alone or + Adrenaline
   b- Exophthalmos of Hyperthyroidism

II- Mydriatics

(↑ Sympathetic or ↓ Parasympathetic)

A) Sympathomimetics (Non-Catecholamines)

1- ↑ α_1-**Adenoceptors in**:
   a- D.P.M. → Active Mydriasis (Preservation of Light Reflex) & ***NO*** Cycloplegia.
   b- B.V. → V.C. → Decongestion & ↓ I.O.P.
2- **Examples**:
   a- Direct: Phenylephrine 1 – 2 %
   b- Indirect: Amphetamine & Hydroxy-amphetamine
   c- Dual (Mixed): Ephedrine 3 – 5 %
3- **Therapeutic use**: Fundus examination specially in elderly patients liable for glaucoma

B) Cocaine:

1- **Surface anesthesia** → Loss of Sensory reflex (Corneal & Conjunctival Reflexes)
2- **Indirect Sympathomimetic** → ↓ Neuronal Uptake-1 (Mainly) + MAO Inhibitor → ↑ Endogenous Noradrenaline → ↑ α_1-receptors → Active Mydriasis & Decongestion.

C) Parasympatholytics:

1- **Block M.R. in**:
   a- C.P.M. → Passive Mydriasis → -ve Light Reflex
   b- Ciliary Muscle → Cycloplegia → Close Canal of Schlemm → ↑ **I.O.P.**
   → Narrow Angle of Filtration & Spaces of Fontana
   → Loss of Accomodatio to Near Vision
   c- ↓ Lacrimation + ***No*** effect on conjunctival B.V. (***No*** parasympathetic tone)
2- **Examples**:
   a- Natural Belladonna Alkaloids: Atropine (1 %) & Hyoscine (1/4 %)
   b- Synthetic Atropine Substitutes:
      - Homatropine (2%), Cyclopentolate (1/2-1%) & Tropicamide (1/2-1%) → Cycloplegia
      - Eucatropine (2 – 5 %) → ***NO*** Cycloplegia
3- **Therapeutic Uses**:
   a- Atropine in Iritis & Corneal Ulcer.
   b- Synthetic substitutes in Fundus examination
4- All are contraindicated in Glaucoma

D) Ganglion Blockers → Systemic Effect

They block Ciliary ganglia → ↓ Parasympathetic → Atropine like → Passive mydriasis + Cycloplegia + ↑ IOP.

NB) Drugs Affecting the Eye as a Systemic Side Effect:

a- Morphine b- Ganglion Blockers c- Sympathoplegics e.g. Reserpine

Treatment of Glaucoma

A) Narrow (Closed) Angle Glaucoma:

Acute Congestive Glaucoma = Medical Emergency

1- **Miotic Eye Drops**:

a- They ↑ Drainage of Aqueous humour

b- Pilocarpine (1-2%) + Physostigmine (1/2%)

c- Better avoid organophosphorus → More congestion

2- **Carbonic Anhydrase Inhibitors**:

a- They ↓ Synthesis of Aqueous humour

b- Acetazolamide *(Diamox)* or Dichlorphenamide → Orally or I.V.

3- **Osmotic Agents** = **Dehydrating Agents** :

a- Imbibe water from Aqueous humour

b- Mannitol (I.V.) or Glycerin (Orally)

B) Wide (Open) Angle Glaucoma:

- Simple & Chronic due to clogging of Spaces of Fontana & Canal of Schlemm
- Management → Either Surgical (Iridectomy) or Medical Treatment:

1- **Miotic Eye Drops**:

a- Short Acting → Pilocarpine or Physostigmine or Demecarium

b- Better avoid long use of organophosphorus compounds → May cause Cataract.

2- **Carbonic Anhydrase Inhibitors**:

a- Systemic: Acetazolamide & Dichlorphenamide.

b- Topical eye drops: Dorzolamide (2 %) & Brinzolamide.

3- **Sympathomimetics**:

a- V.C. → ↓ Synthesis of Aqueous humour.

b- Adrenaline (0.05-2%) & Dipivefrin 0.1% (Stable lipophilic prodrug → Adrenaline)

4- **β-Blockers**:

a- Block β-receptors → ↓ cAMP → ↓ Formation of Aqueous humour

b- Timolol, Betaxolol, Levobunolol, Befunolol & Metipranolol

c- They do not affect size of pupil or ciliary muscle

d- Absorbed from eye → Systemic effect → Affect Heart &Bronchi

5- **α_2-Agonists**:

a- ↑ α_2-receptors → ↓ cAMP → ↓ Formation of Aqueous humour

b- Apraclonidine & Brimonidine

6- **Guanethidine** (10 %) Eye Drops:

a- Miosis → ↑ Drainage of aqueous humour

b- May be used alone or with adrenaline

7- **Prostaglandins**:

a- ↑ Drainage of aqueous humour

b- Latanoprost ($PGF_{2\alpha}$)

NB) Drugs that ↑ I.O.P. = Contraindicated in Glaucoma:

1- Parasympatholytics: Atropine & Its synthetic substitutes.
2- Atropine-like drugs:
   a- Ganglion blockers
   b- Some of Antihistaminics e.g. Diphenhydramine
   c- Tricyclic anti-depressants e.g. Amitriptyline
   d- Anti-arrhythmics e.g. Disopyramide
3- Nitrates → Retinal V.D. & congestion
4- Glucocorticoids.

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NB) Drugs Toxic To The Eye → Iatrogenic Eye Diseases

1- Atropine → Glaucoma
2- Nitrates → ↑ I.O.P.
3- Glucocorticoids → Glaucoma & Cataract
4- Chlorpromazine → Corneal & Lens opacities
5- Thioridazine → Retinopathy
6- Amiodarone → Corneal deposits
7- Oxygen → Retrolental fibroplasia
8- Chloroquine → Retinopathy
9- Ethambutol → Optic neuritis
10- Vioform → Subacute Myelo-Optic Neuropathy (SMON syndrome)
11- Methyl alcohol → Formaldehyde → Toxic to retina & Optic nerve.
12- Digitalis → Yellow vision

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NB) Conjunctival Irritants:

1- Ethyl morphine → Hyperemia → ↑ Healing of cornea ulcer.
2- Chloro-aceto-phenone → ↑ Lacrimation →Tear gas (Lachrymator).

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NB) Local Anesthesia on Eye:

1- Surface anesthetics: Cocaine (Mydriasis) & Tetracaine (No Mydriasis)
2- Infiltration anesthesia (Retrobulbar anesthesia): Procaine & Lidocaine (Xylocaine)

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NB) Anti-Allergic Drugs on The Eye:

1- Anti-histaminics (H_1-blockers) e.g. Antazoline & Levocabastine (0.05 %)
2- Glucocorticoids e.g. Cortisol → Long use → Glaucoma, Cataract & ↑ Infection (Due to ↓ Immunity).
3- Mast Cell Stabilizers e.g. Nedocromil eye drops (2 %)
4- Decongestants e.g. Naphazoline & Tetrahydrozoline

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NB) Anti-inflammatory Drugs On The Eye:

1- Non-Steroidal Anti-Inflammatory Drugs (NSAID) e.g Diclofenac & Ketorolac
2- Steroidal Anti-Inflammatory drugs e.g. Cortisol

NB) Treatment Of Eye Infection:

1- Anti-Bacterial: Sulfacetamide, Tetracyclines, Chloramphenicol & Gentamicin.
2- Anti-Viral: Acyclover & Idoxuridine in Herpe simplex.
3- Anti-Fungal: Amphotericin B, Ketoconazole & Miconazole
4- Boric acid (4 %) irrigation in conjunctivitis.
5- Zinc sulfate in angular conjunctivitis.

NB) Diagnostic Agents on The Eye:

1- Fluorescein → Stain corneal ulcer
2- Hydroxy-Amphetamine → Indirect sympathomimetic → Differentiate between Pre-ganglionic & Post-ganglionic Horner's syndrome (↓ Sympathetic to the face):
   a- Pre-ganglionic Horner's → Post-ganlionic Adrenergic nerve endings are intact → Hydroxyamphetamine → Release Noradrenaline → Mydriasis.
   b- Post-ganglionic Horner's → No Adrenergic Nerve ending → Hydroxyamphetamine → No effect.

Pheochromocytoma

- Tumor usually in adrenal medulla secreting mainly noradrenaline (90%), adrenaline & dopamine.
- It causes → Hypertension, tachycardia, arrhythmia & sweating.
- It may be *Sustained* or *Paroxysmal* (Bouts).

** Diagnosis:*

1- Chemical: Estimation of circulating & urinary catecholamines & their metabolites e.g. Metanephrine, Normetanephrine & Vanil mandelic acid (Normally 2-6.5 mg/24 h urine)

2- Pharmacological:

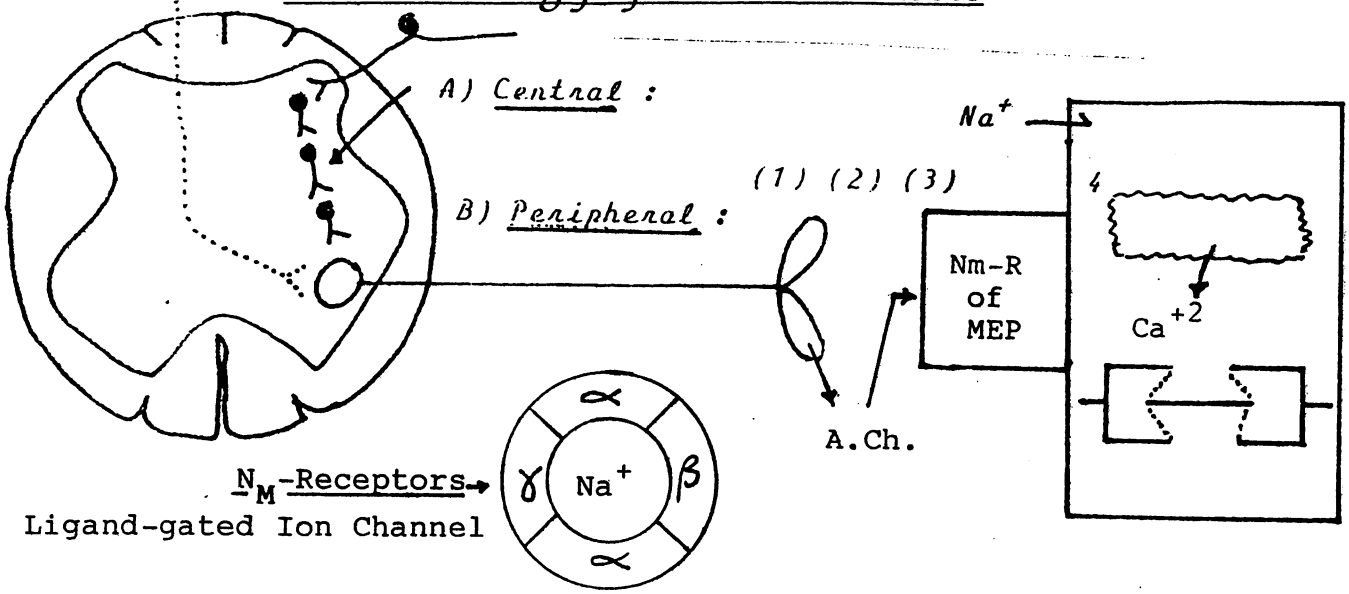
a- Sustained hypertension → I.V. Phentolamine → Sustained drop of blood pressure.
b- Paroxysmal (Bouts) of hypertension → Provocative test → Methacholine or Histamine → Hypertension.
c- Clonidine suppression test → ↓ Sympathetic tone But Not Pheochromocytoma.

** Treatment:*

1- Surgical removal of the tumor:
   a- Pretreatment by Phenoxybenzamine to prevent intra-operative hypertension
   b- Dopamine to treat postoperative hypotension.

2- Medical Treatment:
   a- α-Blocker (Phenoxybenzamine or Prazosin) ± β-Blocker (Propranolol)
   b- α + β Blocker e.g. Labetalol
   c- Metyrosine → ↓ Synthesis of catecholamines
   d- Meta-iodo-benzyl-guanidine → ↓ Release of catecholamines.

Pharmacology of Skeletal Muscle



Skeletal Muscle Relaxants

A) Central Muscle Relaxants:

They inhibit polysynaptic pathway between Dorsal Horn Cells (Sensory) and the Anterior Horn cells (Motor) → ↓ Skeletal muscle tone without affecting voluntary activity.

1- Baclofen	2- Benzodiazepines	3- Barbiturates
4- Tizanidine	5- Mephenesin	6- Methocarbamol
7- Carisoprodol	8- Orphinadrine	9- Thiocolchicoside

B) Peripheral Muscle Relaxants:

1- Drugs that ↓ Synthesis of A.Ch.:

a- Hemicholinium → ↓ Neuronal uptake of choline

b- Triethylcholine → ↓ Utilization of choline by Choline-Acetyl-Transferase (CAT)

2- Drugs that ↓ Release of A.Ch.:

a- Local anesthetics e.g. Procaine.

b- Botulinium toxins.

c- ↓ Ca^{2+}, ↑ Mg^{2+}, or ↑ Phosphate.

3- Neuro-Muscular Blockers: All are Quaternary Ammonium Compounds – $\overset{|}{\underset{|}{N^+}}$ -

a- Competitive N-M Blockers: Compete with A.ch. for N_M-receptor of Sk.m.

- d-Tubocurarine	- Metocurine	- Alcuronium	- Gallamine
- Pancuronium	- Vecuronium	- Atracurium	- Mivacurium

b- Depolarizing N-M Blockers: Act by maintained depolarization

- Succinylcholine - Decamethonium

4- Direct Muscle Relaxant: ↓ Release of Ca^{2+} from sarcoplasmic reticulum.

Dantrolene → The only one that affect direct excitability of Sk.m.

Competitive N-M Blockers

1- They compete with A.Ch. for N_M-receptors of Motor End Plate.
2- They are Antagonists → No Efficacy → Paralysis withOUT Initial twitches.
3- They are antagonized by Anti-Ch.E. e.g. Neostigine

1- *d-Tubocurarine (Curare)*

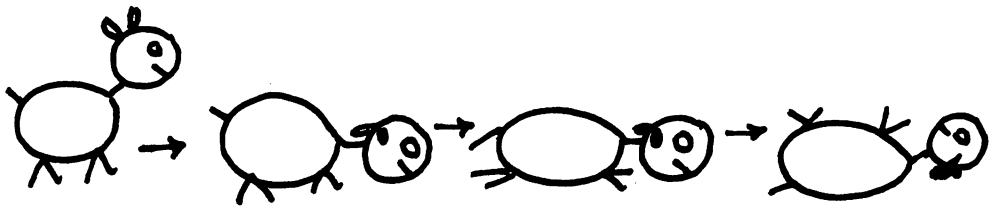
Natural Quaternary ammonium compound (- $\overset{+}{N}$ -) of plant origin

* *Pharmacokinetics:*

1- Not effective orally. Injected I.V.
2- Dose NOT pass B.B.B. & distributed Extracellularly. # C.N.S. # Cell
3- Partially metabolized in liver.
4- Partially excreted unchanged in urine & bile.

* *Pharmacodynamics:*

1- Competitive N-M blocker → Skeletal muscle paralysis
   a- Compete with A.Ch. for N_M-receptors at motor end plate.
   b- Muscle paralysis with**out** initial stimulation (muscle twitches).
   c- Muscle paralysis in special sequence: Fine muscles of face and neck supplied by cranial nerves → Limb & Trunk → Intercostals → Lastly the Diaphragm. Extent of muscle paralysis can be controlled by the dose of Curare.
   d- Recovery occurs in a Reverse direction.
   e- I.V. Curare → Onset (1 min) → Maximum Paralysis (4-5 min) → Duration = Recovery (20-60 min)



2- Weak ganglion blocking effect
3- Histamine release → V.D. & Bronchospasm
4- Hypotension: Ganglion Blocker + Histamine release + Muscle paralysis → ↓ V.R.
5- No C.N.S. actions - $\overset{+}{N}$ -

* *Therapeutic Uses:* 15 – 20 mg I.V.

1- Adjuvant during general anesthesia
2- ↓ Spontaneous respiration → Facilitate artificial respiration by
3- Spastic conditions e.g. Tetanus and resistant Status Epilepticus
4- Diagnosis of Myasthenia gravis → Supersensitivity

* *Drug Interactions of Curare:*

A) Drugs that Potentiate Curare → Decrease the dose of Curare

1- General anesthesia: Ether, Halothane, Isoflurane & Enflurane
2- Local Anesthesia e.g. Procaine.
3- Antibiotics e.g. Aminoglycosides → Streptomycin
4- Anti-Arrhythmics e.g. Quinidine
5- Anti-Psychotics e.g. Phenothiazines → Chlorproazine
6- Hypokaleia (↓ K^+)
7- Acidosis (↓ pH)

B) Drugs that Antagonize Curare:

1- Anticholinesterases e.g. Neostigmine (Antidote) & Edrophonium.
2- Potassium (K^+) → Direct muscle stimulant.
Curare does not affect direct muscle excitability

* *Toxicity of Curare:*

1- ***Apnea*** due paralysis of respiratory muscles
2- Hypotension, Bronchospasm & Allergy.

* *Treatment of Curare Poisoning:*

1- Artificial respiration.
2- ***Neostigmine*** 1-3 g I.V. → Specific antidote.
If excess Neostigmine → Excess A.Ch. → Depolarizing block.
3- ***Atropine*** 0.5 – 1 mg I.V. → Before Neostigmine → To block the unwanted muscarinic actions of Neostigmine.
If Atropine after Neostigmine → Severe initial bradycardia
4- ***Edrophonium*** 10 mg I.V. to initiate treatment.
If Edrophoniu alone → Repeated injections or I.V. infusion.
5- If hypotension → Vasopressors
6- If Bronchospasm or Allergy → Antihistamine (H_1-Blocker).

2- *Metocurine (Metubine)*

1- Semi-synthetic derivative of Curare.
2- **Stronger** than Curare (4 times) as muscle relaxant.
3- **Less** Ganglion blocker } - **Less** Hypotension
4- **Less** Histamine release } - **Less** Bronchospasm

3- *Alcuronium (Alloferin)*

1- Semi-synthetic derivative of Curare.
2- **As** potent as curare as muscle relaxant
3- **No** ganglion block } - **No** Hypotension
4- **No** Histamine release } - **No** Bronchospasm

All of the following N- M blockers are synthetic Quaternary ammonium compounds

4- Gallamine (Flaxidil)

1- Synthetic quaternary ammonium compound
2- Weaker than Curare (1 : 5) & Shorter duration
3- Tachycardia:
   a- Selective block of cardiac M_2-receptors → Atropine like on heart
   b- ↑ Release of Noradrenaline
   c- Avoid in patients with tachycardia e.g. Thyrotoxicosis
4- No Ganglion block & No histamine release → No Hypotension
5- No hepatic metabolism → Only Renal excretion → Avoid in renal patients

5- Pancuronium (Pavulon)

1- Synthetic steroid quaternary ammonium compound
2- Stronger than Curare (6 : 1) as muscle relaxant.
3- No Ganglion block } - No hypotension
4- No Histamine release } - No bronchospas
5- Tachycardia → ↑ Release of Noradrenaline & Anticholinergic.
6- Hepatic metabolism (25 %) & Renal excretion (75 %)

6- Vecuronium (Norcuron)

1- Synthetic Steroid quaternary ammonium compound
2- Stronger than Curare (6 : 1) & Shorter duration (15 minutes) as muscle relaxant.
3- No Ganglion block } - No Hypotension
4- No Histamine release } - No Bronchospasm
5- No Anticholinergic } - No Tachycardia
6- Hepatic metabolism (35 %), Biliary excretion (50 %) & Renal excretion (15 %).

7- Atracurium (Tracrium)

1- Synthetic Isoquinoline Quaternary ammonium compound
2- Slightly Stronger & Shorter than Curare
3- No Ganglion Block + Slight Histamine release + No Anticholinergic
4- No Hepatic Metabolism & No Renal excretion → Allowed in patients with hepatic &/or Renal diseases
5- Spontaneous hydrolysis → Hofmann elimination

8- Mivacurium

1- Synthetic Isoquinoline Quaternary ammonium compound related to Atracurium
2- Stronger than Curare (4 : 1)
3- Shortest duration of action (10 – 20 minutes).
4- Metabolized by Pseudo-Ch.E.
5- No Ganglion block + Mild histamine release + No Anticholinergic.

Depolarizing N-M Blockers

1- They act through prolonged Depolarization of the motor end plate.
2- They produce initial depolarization (Stimulation & Twitches) followed by maintained depolarization (Block & Paralysis).
3- They are Partial agonists = Dualist
4- They are Potentiated by Anti-Ch.E. → More depolarization

	Competitive *(Non-Depolarizing)*	Depolarizing *(Non-Competitive)*
1- Example:	Curare	Succinylcholine
2- Mechanism:	Competes with A.Ch. for N_M-R	Maintained depolarization
3- Nature:	Antagonist	Partial agonist (Dualist)
4- Block:	Reversible Competitive	Reversible Non-competitive
5- Effect:	Paralysis without twitches	Twitches → Paralysis
6- Neostigmine:	Antagonize	Potentiated

1- *Succinylcholine (Suxamethonium)*

Synthetic choline ester quaternary ammonium compound

* *Pharmacokinetics:*

1- Not effective orally. Injected I.V.
2- No B.B.B. & Distributed Extracellularly
3- Rapidly hydrolyzed by Pseudo-Ch.E. (but slower than A.Ch.) → Succinic acid + Succinyl-monocholine (Very weak competitive N-M Blocker) → Succinic acid + Choline (Inactive)
4- Short duration of action (5 – 10 minutes).

* *Pharmacodynamics:*

1- Depolarizing N-M Blocker:
   a- Initial muscle twitches → Followed by → Paralysis
   b- It produces 2 Phases of Block

	Phase I	Phase II
1- Mechanism:	Depolarization	Desensitization
2- Anti-Ch.E.	Potentiation	Antagonism

2- Ganglion Stimulant effect:
   a- Initial ↑ Parasympathetic → Bradycardia (Avoid in Heart block) & ↑ Salivation. Pretreatment with Atropine.
   b- Then ↑ Sympathetic → Tachycardia & Hypertension.

3- Mild release of Histamine.

* Therapeutic Uses of Succinylcholine:

1- Facilitate Endoscopy e.g. Endotracheal intubation
2- During Electro-Convulsive Therapy in Psychiatry
3- Orthopedic manipulations e.g. correction of Dislocation
4- Diagnosis of Myasthenia gravis → Initial improvement then → worsening

* Toxicity of succinylcholine:

1- Prolonged Apnea due to abnormal Pseudo-Ch.E. activity:
   a- Idiosyncrasy → Genetic abnormality in Pseudo-Ch.E. → Abnormal Dibucaine number.
   b- Liver disease & Malnutrition → ↓ Synthesis of Enzyme
   c- Hemorrhage & burn → Loss of Enzyme
   d- Anti-Ch.E. e.g. Organophosphorus poisoning → ↓ Enzyme

♦ Treatment of Succinylcholine Apnea:
   a- Artificial respiration
   b- Fresh blood transfusion

2- Malignant Hyperthermia → Genetic abnormality in Sarcoplasmic reticulum → Excess release of Ca^{2+} → Muscle rigidity, ↑ Heat production, Lactic acidosis & ↑ CPK.

♦ Treatment of Malignant hyperthermia:
   a- I.V. Dantrolene b- Cooling c- Correct acidosis

3- Muscle pain 4- Hyperkalemia

5- ↑ I.O.P. 6- ↑ Intra-gastric pressure

2- *Decamethonium* (C-10)

1- Synthetic methonium (- $\overset{|}{\underset{|}{N^{+}}}$ -) related to ganglion blockers
2- Depolarizing N-M blocker
3- Its antidote is Pentamethonium (C-5, Competitive ganglion blocker)

Direct Skeletal Muscle Relaxant

Dantrolene (Dantrium)

1- Hydantoin derivative related to Phenytoin
2- Direct Sk.m. relaxant
3- It *blocks Ryanodine* receptors of *Sarcoplasmic reticulum* → *↓ Release of Ca^{2+}*.
4- ↓ Direct excitability of Sk.m.
5- Very weak effect on smooth & cardiac muscles
6- Therapeutic uses:
   a- Orally in *Spastic* muscle lesions
   b- I.V. to treat *Malignant hyperthermia* of Succinylcholine & Halothane
   c- I.V. to treat *Neurolept Malignant Syndrome* of Antipsycholtic drugs
7- Adverse effects → Drowsiness, Diarrhea & Damage of liver

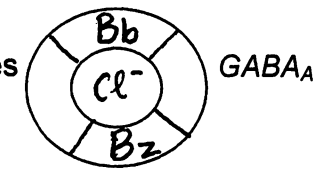
Central Muscle Relaxants

- They ↓ Spinal & Supra-spinal Polysynaptic pathways → ↓ Skeletal muscle tone without affecting voluntary activity.
- They are useful in treatment of painful skeletal muscle spasm & stiffness

1- Barbiturates e.g. Phenobarbitone

a- Bind to specific Barbiturate receptors → Facilitate GABA-A Transmission → ↑ Cl^- influx → Hyperpolarization → Post-synaptic inhibition.

b- Inhibit BOTH Poly-synaptic & Mono-synaptic spinal reflexes



$GABA_A$

2- Benzodiazepines e.g. Diazepam & Clonazepam

a- Bind to specific Benzodiazepine receptors → Facilitate GABA-A Transmission → ↑ Cl^- influx → Hyperpolarization → Post-synaptic inhibition.

b- Inhibit BOTH Poly-synaptic & Mono-synaptic spinal reflexes

3- Baclofen (Lioresa);

a- Synthetic GABA derivative BUT → Effective Orally & Passes B.B.B.

b- Direct ↑ GABA-B receptors:
- ↓ Ca^{2+} influx → Presynaptic inhibition
- ↑ K^+ Efflux → Hyperpolarization

c- Inhibit BOTH Poly-synaptic & Mono-synaptic spinal reflexes

4- Tizanidine → ↑ α_2-receptors in C.N.S. → Muscle relaxation

5- Mephenesin (Decontractyl):

a- Chemically related to Meprobamate (Minor Tranquillizer).

b- ↓ **Poly**synaptic spinal reflexes **ONLY**.

c- No effect on Monosynaptic reflexes → No effect on stretch reflex.

d- Therapeutic uses:
- a- Strychnine poisoning → Specific antidote.
- b- Painful muscle spasm & stiffness

6- Methocarbamol (Robaxin): Related to Mephenesin But Stronger & Longer

7- Carisoprodol (Carisoma):

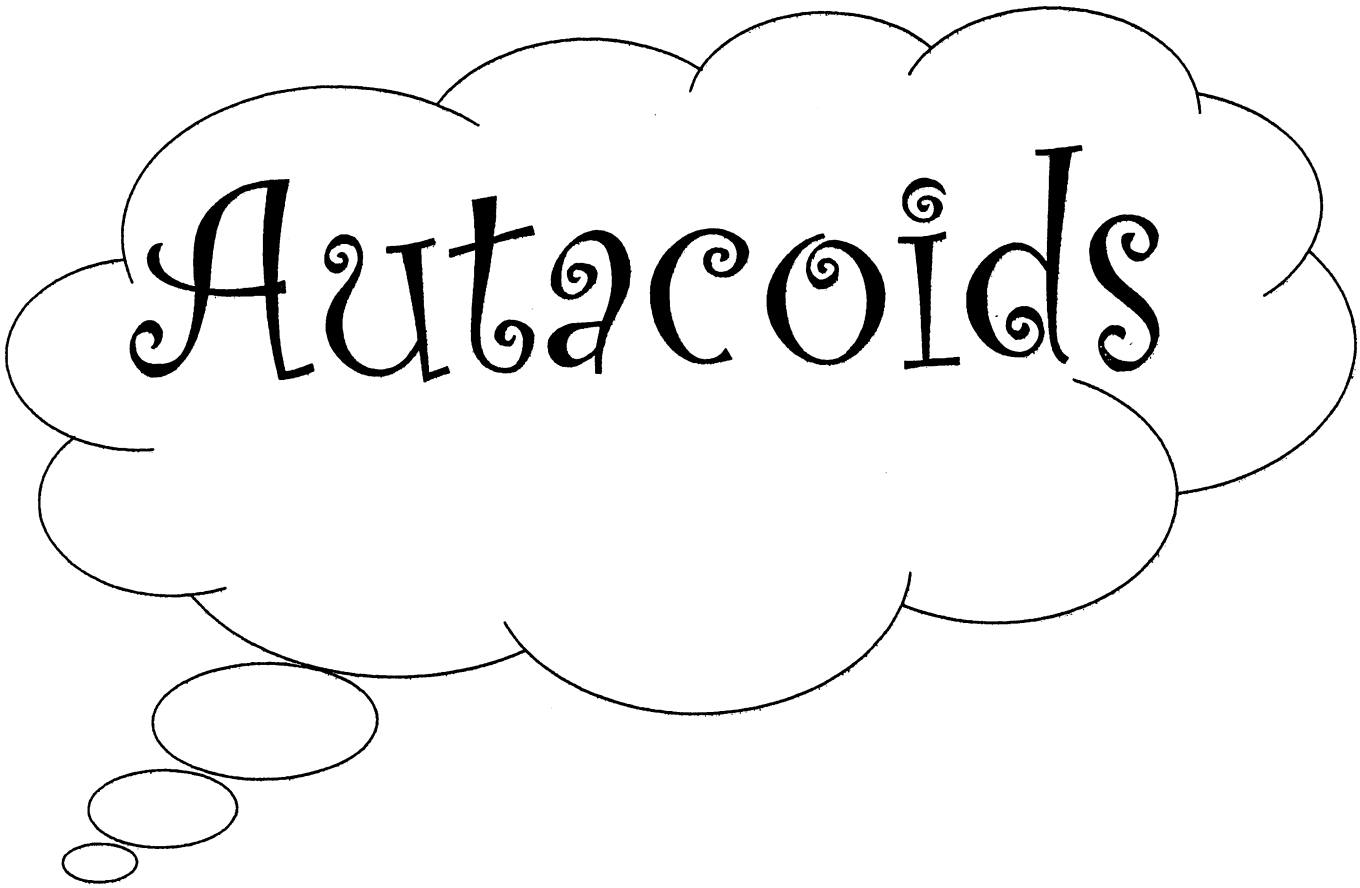
a- Related to Mephenesin But ↓ Both Mono- & Poly-synaptic spinal reflexes

b- Produces Drowsiness & Hypnosis → Avoid car driving

Anti-Spasticity Agents = Spasmolytics

1- Drugs used to treat skeletal muscle spasm & stiffness.

2- They include:
- a- Central Muscle Relaxants
- b- Dantrolene


Autacoids

Autacoids

Active substances in the body

I- Atrial Natriuretic Peptide (ANP):

1- Polypeptide released from Atrium → ↑ G.F.R. → ↑ Na^+ excretion in urine.
2- ↓ Renin & ↓ Aldosterone.

II- Vaso-Active-Intestinal Polypeptide (VIP):

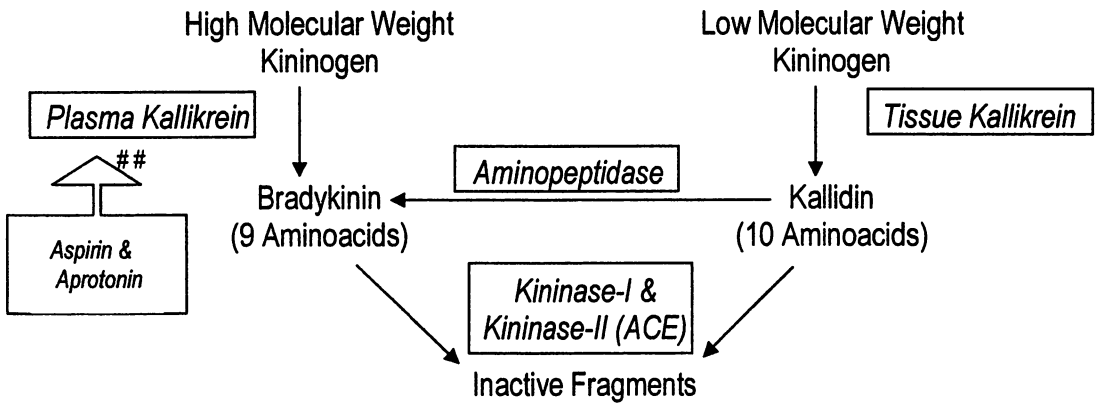
1- Polypeptide → Chemical transmitter in C.N.S. & Periphery.
2- Smooth muscle relaxation → V.D., Relax G.I.T. & *Bronchodilatation*.

III- Substance-P:

1- Polypeptide → 11 Amino-acids.
2- Metabolized by A.C.E.
3- V.D., ↑ Intestinal motility & Bronchospasm.
4- Pain transmitter at Substania Gelatinosa in Spinal Cord.
5- Opioids (e.g. Morphine), and Endorphins & Enkephalins → ↑ Opiate receptors → ↓ Release of Substance-P → Analgesia.

IV- Kinins:

Polypeptides:
1- Bradykinin → Nonapeptide (9 Amino-acids).
2- Kallidin → Decapeptide (10 Amino-acids).



1- Aspirin & Aprotonin (Trasylol) → ↓ Kallikrein enzymes → ↓ Synthesis of Kinins.
2- Rapid metabolism by Kininase enzymes → Short duration of action (t1/2 < 15 Seconds).
3- Kininase-II = Angiotensin Converting Enzyme (ACE).
4- A.C.E. Inhibitors e.g. Captopril → ↑ Kinins → V.D.

* Pharmacological Actions of Kinins:

They ↑ specific B_1 & B_2 receptors coupled to G-proteins

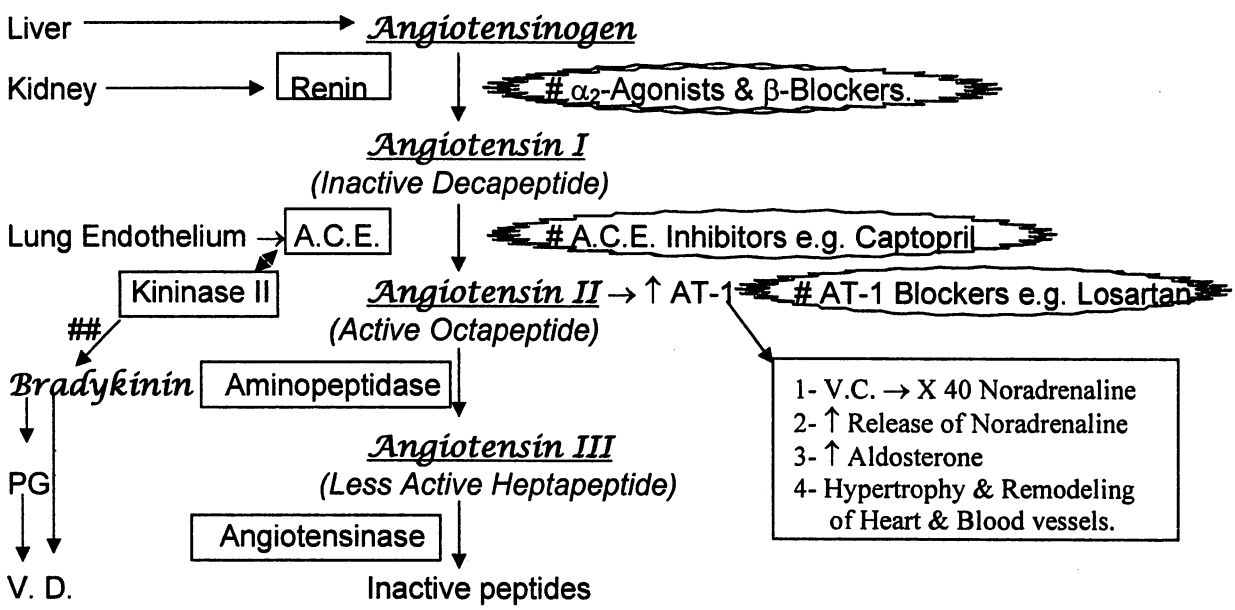
1- Powerful *Arteriolar V.D.* (10 times > Histamine)
   They ↑ B-receptors & ↑ PG → ↓ Bl.p. & Redness & Hotness.
2- Venous V.C. → ↑ Venous pressure. } Edema formation.
3- ↑ Capillary permeability
4- Stimulate Sensory Nerve Endings → Pain.
5- Important mediator of *Inflammation* & *Anaphylaxis*.
6- Tachycardia: Direct effect on heart + Reflex from hypotension.
7- Spasmogenic on smooth muscle → Bronchospasm.

V- *Angiotensins*:

Polypeptide autacoids:

1- Angiotensin-I: *In*active decapeptide (10 Aminoacids).
2- Angiotensin-II: *Very Active* Octapeptide (8 Aminoacids).
3- Angiotensin-III: *Less* active Heptapeptide (7 AMinoacids).

Renin-Angiotensin-Aldosterone-System (RAAS)



A) Angiotensinogen:

1- α_2-Globulin synthesized in Liver mainly.
2- Substrate for Renin enzyme.
3- ↑ Synthesis by:
   a- Hormones: Thyroid, Cortisol & Estrogen.
   b- Angiotensin-II.

B) Renin:

1- Protease enzyme synthesized & secreted by Juxta-Glomerular Cells.
2- ↑ Renin Secretion of by:
   a- ↓ Pressure in Afferent Glomerular Arterioles (↓ Blood volume or Bl.p.).
   b- ↓ Na^+ in Macula densa (Part of Distal Convoluted Tubules).
   c- ↑ Sympathetic β_1-Receptors.
   d- Prostaglandins e.g. PGA, PGE & PGI_2 (Prostacyclin).
   e- ACE Inhibitors e.g. Captopril.
3- ↓ Renin Secretion by:
   a- β_1-Blockers: Atenolol, Propranolol & Labetalol.
   b- α_2-Agonists: Clonidine & α-Methyl Dopa.
   c- ↑ K^+ in plasma d- Angiotensin-II e- Vasopressin (ADH)
4- Renin Receptors Blockers: Enalkiren & Remikiren.

C) Angiotensin Converting Enzyme (A.C.E.):

1- ACE = Kininase-II = Dipeptidyl Carboxy-peptidase.
2- Present in capillary endothelium especially in the lung.
3- Converts the *Inactive* Angiotensin-I to Very *Active* Angiotensin-II.
4- Metabolizes other autacoids e.g. Bradykinin & Substance-P.
5- ACE Inhibitors e.g. Captopril, Lisinopril & Enalapril (See CVS).

D) Dynamics of Angiotensins:

1- They stimulate specific AT-receptors:
   a- AT-1 → ↑ G_q-protein → ↑ PLC → ↑ IP_3 & DAG → ↑ Ca^{2+} & ↑Protein kinases → Most of actions of Angiotensin.
   b- AT-2 present in C.N.S. & Adrenal medulla.
2- *Powerful V.C.* → 40 times > Noradrenaline.
3- ↑ Release of Noradrenaline, ↑ Sympathetic ganglia & Adrenal medulla → ↑ Sympathetic activity.
4- ↑ Biosynthesis & Secretion of Aldosterone.

} Hypertension

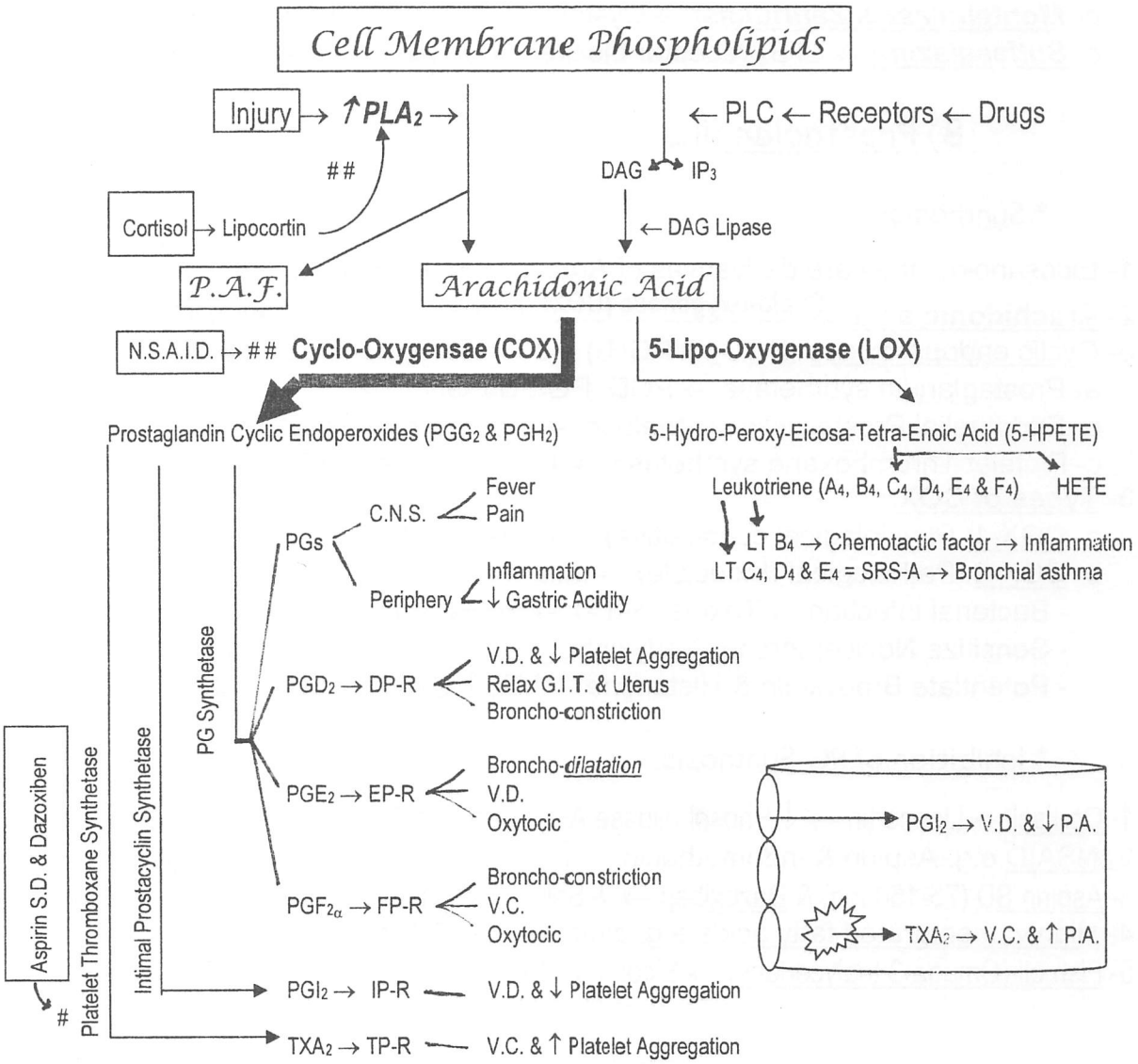
5- ↓ Renin secretion & ↑ Angiotensinogen.
6- +ve Inotropic effect.
7- Mitogenic effect → Hypertrophy & Remodeling of Heart & Blood vessels.
8- Spasmogenic effect on smooth muscles.
9- C.N.S. → ↑ ADH, ↑ ACTH & Dipsogenic effect (↑ Drinkining).
10- Its amide derivative is used in treatment of severe *Hypotension* especially induced by α-blockers.

E) Renin-Angiotensin-Aldosterone-Systemic Inhibitors (RAAS-I):

1- ↓ Renin Secretion: β-Blockers & α_2-Agonists.
2- Renin-receptor Blockers: Enalkiren.
3- ACE Inhibitors: Captopril, Lisinopril & Enalapril.
4- AT_1-Receptors blockers: Losartan, Valsartan, Candesartan & Telmisartan.

VI- Eicosanoids

- They include → Prostaglandins (PG) & Leukotrienes (LT).
- They have very short duration of action.
- They are synthesized & released as required. Not stored in body.
- Synthesized by All cells from Arachidonic acid.
- Arachidonic acid is synthesized from cell membrane phospholipids:
  1- One Step by Phospholipase A_2 (# by Lipocortin of Cortisol).
  2- Two Steps by Phospholipase C *then* Di-acyl-glycerol (DAG) lipase.



A) Leukotrienes ($LTA_4 \rightarrow LTF_4$)

1- *Arachidonic acid* derivatives.
2- Synthesized by ***Lipo-Oxygenase*** enzymes (***5-LOX***, 12-LOX & 15-LOX).
3- **LTB_4** → Leukocytic Chemotactic Factor → ***Inflammation*** e.g. Ulcerative colitis.
4- **Cysteinyl-Leukotrienes (LTC_4, LTD_4 & LTE_4)** = Slow Reacting Substance of Anaphylaxis (SRS-A) → Powerful (1000 > Histamine) Bronchospasm, ↑ Bronchial secretions & ↑ Exudation of plasma → ***Bronchial Asthma***.
5- Leukotrienes Antagonists:
   a- ***Zileuton*** → ↓ 5-LOX → ↓ Synthesis of Leukotrienes.
   b- ***Montelukast & Zafirlukast*** → Cysteinyl-LT receptor blockers.
   } *Useful in Aspirin-induced Asthma.*
   c- ***Sulfasalazine*** → LTB_4-receptor blocker → Useful in Ulcerative colitis.

B) Prostaglandins

* Synthesis:

1- Eicosanoids, they are derivatives of Arachidonic (eicosanoic) fatty acid.
2- **Arachidonic acid** —***Cyclo-oxygenase (COX)***→ Cyclic endoperoxides (PGG_2 & PGH_2).
3- Cyclic endoperoxides (PGG_2 & PGH_2) are further metabolized by:
   a- Prostaglandin synthetase → PGD, PGE & PGF.
   b- Endothelial Prostacyclin synthetase → Prostacyclin (PGI_2).
   c- Platelet Thromboxane synthetase → Thromboxane A_2 (TXA_2).
3- **Types of COX**:
   a- COX-1: Physiological constitutive) → Renal VD & ↓ Gastric HCl.
   b- COX-2: Pathological (Inducible) → Inflammation:
      - Bacterial infection → Toxins → IL-1 → PGE_2 → Hypothalamic HRC → Fever.
      - Sensitize Nociceptors to Bradykinin, Histamine & 5-HT → Pain.
      - Potentiate Bradykinin & Histamine → VD, ↑ Capillary permeability → Edema.

* Inhibition of PG Synthesis:

1- Cortisol → Lipocortin → ↓ Phospholipase A_2 → ↓ Arachidonic acid (↓ PGs & LTs) & PAF.
2- NSAID e.g. Aspirin & Indomethacin → ↓ COX centrally & peripherally.
3- Aspirin SD (75-150 mg) & Dazoxiben → ↓ Selectively platelet thromboxane synthetase.
4- Highly unsaturated fatty acids e.g. oleic, linoleic & lanolinic acids.
5- Fish oil (Omega-3 triglycerides) → Eicosa-penta-enoic acid → Abnormal PGs & TXA_2.

* Actions PGs:

They ↑ specific membrane-bound *receptors coupled to G-proteins* (DP-R, EP-R, FP-R, IP-R & TP-R) → Affect Adenylate cyclase & Phospholipase C enzymes.

1- **C.N.S.**:
   a - Thalamus → Pain transmission.
   b - Hypothalamus → HRC → Fever.
2- **Eye** → ↑ Outflow of Aqueous humor → ↓ I.O.P.
3- **Inflammation** (see before).
4- **Immunomodulation**. PGE_2 → ↓ T-cell proliferation.
5- **C.V.S.**:
   a- Maintain the patency of ductus arteriosus during fetal life.
   b- Blood Vessels:
      - Most of them e.g. PGD_2, PGE_2 & PGI_2 → VD.
      - TXA_2 → VC.
   c- Platelets:
      - PGI_2 & PGD_2 → ↓ Platelet aggregation.
      - TXA_2 → ↑ Platelet aggregation.
5- **Bronchi**:
   a- Most of them e.g. $PGF_{2\alpha}$ & TXA_2 → Bronchospasm.
   b- PGE_2 → Bronchodilatation.
6- **G.I.T.**:
   a- Stomach → ↓ HCl, ↑ Mucin, ↑ HCO_3^-, ↑ Blood supply & ↑ Healing of ulcer.
   b- ↑ Intestinal motility → Diarrhea.
7- **Kidney**: VD. PGI_2 → ↑ Renin.
8- **Sex organs**:
   a- Uterus → ↑ Contractility & motility.
   b- Essential for V.D. of male genital organs and transport of sperms.
9- **Endocrines**: PGE_2 → ↑ Release of anterior pituitary hormones & ↑ steroidogenesis by the adrenals.

* Therapeutic Uses of PGs:

1- Open angle *Glaucoma* → ***Latanoprost*** eye drops ($PGF_{2\alpha}$ analogue).
2- Maintain the *patency of ductus arteriosus* in infants with transportation of great vessels → PGE_1 (***Alprostidil***) IV infusion.
3- V.D. & ↓ P.A. for *P.V.D.* → PGI_2 (***Epoprostenol & Iloprost***) I.V. infusion.
4- *Bronchial asthma* → PGE_2 may be used *But* irritant.
5- *Peptic ulcer* induced by NSAID : PGE_2 (***Misoprostol & Enprostil***).
5- Induction of therapeutic *abortion*, labor and vaginal contraception → ***Dinoprost*** ($PGF_{2\alpha}$ intraamniotic), ***Dinoprostone*** (PGE_2 vaginal suppository), ***Gemeprost*** (intravaginal) & ***Carboprost*** (IM).
6- Induce erection in *males* → PGE_1 intracavernous.

Prostaglandins

Actions	Uses of PG	Uses of NSAID
1- Mechanism → G-protein coupled receptors		
1- C.N.S.: a- Hypothalamus → HRC → Fever b- Thalamus → Pain		- Antipyretic - Analgesic
2- Eye → ↑ Outflow of Aqueous Humor → ↓ IOP	Open angle glaucoma (*Latanoprost* Eye drops)	
3- Peripheral → Inflammation		- Anti-inflammatory
4- Immunomodulating → ↓ T-lymphocytes		
5- C.V.S.: a- Maintain patency of Ductus Arteriosus b- B.V. → Most of them → V.D. → TXA-2 → V.C. c- Platelets → PGI-2 & PGD-2 → ↓ PA → TXA-2 → ↑ PA	-Maintain patency in transportation of vessels *(Alprostidil I.V. Infusion)* - PVD *(Epoprostenol & Iloprost I.V. Infusion)* - Antiplatelet agent *(Epoprostenol & Iloprost)*	- Patent ductus srteriosus without transportatioin of big vessels - Antiplatelet
6- Bronchi → PGE-2 → Dilatation → PGF-2α → Constriction	- Bronchial asthma *(PGE-2)*	
7- G.I.T. : a- Stomach: ↓ HCl, ↑ HCO_3, ↑ Mucus, ↑ Blood supply & ↑ Healing b- Intsetine → ↑ Motility	- NSAID induced peptic ulcer *(Misoprostol & Enprostil)*	
8- Kidney: V.D. & ↑ Renin		
9- Sex organs: a- Females: Uterine contractions b- Males: Erection & Motility of sperms	- Labor, abortion & contraception *(Dinoprost, Dinoprostone, Gemeprost & Carboprost)* - Improve erection & fertility	- Dysmenorrhea & premature labor
10- Hormones: ↑ Pituitary & ↑ Steroidogenesis		

VII- Platelet Activating Factor (PAF):

1- Derived from cell membrane phospholipids by Phospholipase A_2 enzyme.
2- Important mediator in acute inflammation, anaphylaxis & bronchial asthma.
3- ↑ Platelet aggregation.

* *

VIII- Cytokines:

Biologically active peptides produced by lymphocytes & other cells. They include:

1- **Interleukins (ILs) :** Soluble glycoproteins mediators produced by leukocytes. IL1 is an important mediator in inflammation and rheumatic diseases.
2- **Interferons (IFNα,β γ)** : They are natural proteins produced by virally infected cells. They have a non-specific antiviral activity by ↓ their growth. IFNα-2a IFNα-2b are used SC & IM for treatment of some viral diseases e.g. hepatitis B & C.
3- **Tumor Necrosis Factor (TNF)**.
4- **Colony Stimulating Factors (CSF)**.
5- **Lymphotoxins**.

* *

IX- Serotonin (5-HT, 5-Hydroxy-Tryptamine)

* Synthesis of Serotonin:

Tryptophan

Tryptophan Hydroxylase Enzyme (Rate Limiting Enzyme) ↓ *# Para-Chloro-Phenylalanin. # Para-Chloro-Amphetamine*

5- Hydroxy-Tryptophan → Passes B.B.B.

Aromatic L-Aminoacid Decarboxylase (Dopa Decarboxylase) Present in GIT & CNS NOT Platelets ↓ *# α-Methyl-Dopa*

Serotonin (5-HT) → Can NOT pass B.B.B.

MAO-A | *Pineal Body in CNS*

5-Hydroxy-Indol Acetic Acid = 5-HIAA → Urine (1 – 10 mg / day)

Melatonin (See CNS)

* Kinetics of 5-HT:

1- Not effective Orally.
2- Does Not pass B.B.B. (5-Hydroxy-Tryptophan passes BBB → 5-HT in CNS).
3- Metabolized by MAO-A → 5-Hydroxy-Indol Acetic Acid (5-HIAA) → Urine (1-10 mg/day):
   a- ↑ 5-HIAA in urine: Carcinoid tumor & Reserpine.
   b- ↓ 5-HIAA in urine: α-Methyl-Dopa & MAO-Inhibitors.

* Physiology of serotonin:

1- Biological amine.

2- C. N. S.:

a- Synthesized & stored in C.N.S. → Chemical transmitter.

b- Control of: - Mood & Behavior - Appetite - Body Temperature
- Blood pressure - Pain - Migraine Headache

3- G. I. T.:

a- Synthesis & Storage *Mainly* in Enterochromaffin Cells (90% of 5-HT).

b- Local Hormone → Control of Peristalsis.

3- Platelets:

a- No synthesis, Uptake & Storage *ONLY* (10% 5-HT).

b- Hemostatic → V.C. & ↑ Platelet aggregation.

* Mechanism Of Action Of 5-HT:

- Serotonin stimulates specific 5-HT receptors → 7 Types & many subtypes.
- All 5-HT receptors (Except 5-HT_3) are coupled to G-proteins.
- 5-HT_3 is coupled to ligand-gated ion channel.

1- 5-$HT_{1-A \rightarrow F}$ → G_i → ↓ A.C. → ↓ cAMP. Present in CNS & Periphery:
a- Buspirone → 5-HT_{1A} Partial Agonist → Treat chronic anxiety syndrome.
b- Sumatriptan → 5-HT_{1D} Agonist → Treatment of Acute Migraine Headache.

2- 5-$HT_{2\,A,\,B\,\&\,C}$ → G → ↑ PLC → ↑ IP_3 & DAG → CNS, Smooth muscle & Platelets.

3- 5-HT_3 → Ligand-Gated Ion Channel → CNS (CTZ) & Peripheral neurons (Nociceptors, autonomic & enteric).

4- 5-HT_4 → G_s → ↑ A.C. → ↑ cAMP. Metoclopramide → 5-HT_4 Agonist → Prokinetic agent.

5- $5HT_{5-7}$ in CNS.

* Actions of 5-HT:

1- C. V. S.:

a- 5-HT_1 → + ve Inotropic & +ve Chronotropic → ↑ C.O.P.

b- 5-HT_2 → ↑ Platelet Aggregation & Generalized V.C. especially on Veins.

c- ↑ Presynaptic 5-HT_1 → ↓ Release of 5-HT & N.A. → Coronary & Sk. m. V.D.

d- I.V. → Triphasic effect on Bl.p.:
- Initial ↓ Bl.p. due to ↑ Bezold-Jarisch reflex (5-HT_3).
- *Then* ↑ Bl.p. due to generalized V.C. & ↑ C.O.P.
- *Then* ↓ Bl.p. due to Sk.m. V.D.

2- Anti-Diuretic → Afferent Renal V.C.

3- ↑ Autonomic Ganglia & Adrenal Medulla.

4- Spasmogenic effect on smooth muscles e.g. Bronchi & G.I.T.

5- 5-HT_3 → ↑ Nociceptors → Pain.

* Drugs Affecting Serotonin:

A) 5-HT Receptor Agonist:

1- *Buspirone* → 5-HT_{1A} Partial Agonist → Treatment of Chronic Anxiety syndrome.
2- *Sumatriptan* → 5-HT_{1D} Agonist → Treatment of Acute Migraine headache.
3- *Metoclopramide & Cisapride* → 5-HT_4 Agonists → ↑ Enteric ganglia → ↑ Release of A.Ch. → ↑ Motility of GIT → Prokinetic agent.

B) Selective Serotonin Reuptake Inhibitors (SSRI):

Example: *Fluoxetine* → Anti-depressant.

C) 5-HT Receptors Blockers:

1- *Methysergide*:
- a- Lysergic acid derivative, related to Ergot alkaloids.
- b- Useful in *Prophylaxis* of *Migraine* Headache. Allowed in pregnancy.
- c- Long Use > 6 months → Retroperitoneal, pleural & endocardial *Fibrosis*.

2- *Pizotifen & Cyproheptadine*:
- a- Anti-Serotonin, Anti-Histamine (H_1-blocker) & Anti-Cholinergic (M-Blocker).
- b- Produces → Sedation, Dry Mouth & ↑ Appetite.
- c- Useful in:
  - Anti-Serotonin → *Prophylaxis* of *Migraine* headache & *Carcinoid* tumor.
  - Anti-Histamine → Allergy e.g. Urticaria.
  - Appetizer.

3- *Ondansetron & Granisetron*:
- a- selective 5-HT_3-Blockers → Anti-emetic.
- b- Useful in Cancer chemotherapy-induced vomiting.

4- *Ketanserin*:
- a- 5-HT_2 - Blocker → Mixed V.D. & ↓ Platelet Aggregation.
- b- α_1 - Blocker → V.D.
- c- Anti-Histamine & Dopamine blocker.
- d- Useful in Hypertension & P.V.D.

5- *A.N.S. Drugs*: Ergotamine & Phenoxybenzamine.

6- *C.N.S. Drugs*:
- a- *Anti-psychotics*: Chlorpromazine, Clozapine & Risperidone & Olanzepine.
- b- *Tricylic antidepressants* e.g. Amitriptyline.
- c- *Hallucinogenics* e.g. Lysergic acid diethylamide (LSD).

X- Histamine

1- Biological ***amine***.

2- ***Found*** in Lung, GIT, Skin & Brain:
   a- Present in Mast cells, Basophils, Cells (e.g. Enterochromaffin-like cells & epidermis) & nerve endings.
   b- Mast cells contain Histamine & Heparin in a protein complex.
   c- Mast cells contain Histidine-decarboxylase (synthesizing) & Histaminase (metabolizing) enzymes.

3- ***Synthesis***: Histidine aminoacid —*Histidine decarboxylase*→ Histamine.

* Kinetics of Histamine:

1- *Not* effective Orally → Acetylated by flora & metabolized by gut mucosa & liver. Well absorbed after S.C. & I.M.
2- Does *Not* pass B.B.B.
3- *Fate*:
   a- Major Metabolic pathway → *Methylation*:
   Histamine —*Imidazole N-Methyl Transferase*→ Methyl-histamine → Some → Urine (*MAO or DAO*)
   Methyl-Imidazole Acetic Acid (MIAA) → Major Metabolite in Urine.
   b- Some histamine → Metabolism by Histaminase (Di-Amine Oxidase = DAO) → Imidazole Acetic acid → Urine. Placenta contains excess Histaminase.
   c- In circulation → Binding to plasma proteins = Histaminopexy.
   Histaminopexy is deficient in allergic patients.

* Mechanism O f Action Of histamine:

Histamine stimulates specific H-receptors coupled to G-protein:
1- H_1-receptors → G → ↑ PLC → ↑ IP_3 & DAG → ↑ Ca^{2+} & ↑ Protein kinases:
   a- Smooth muscle → Spasmogenic.
   b- Endothelium → ↑ Nitric oxide → ↑ Guanylate cyclase → cGMP → **V.D.**
2- H_2-receptors → G_s → ↑ Adenylate cyclase → ↑ cAMP → ↑ Heart, ↑ HCl & V.D.
3- H_3-receptors → G_i → ↓ Adenylate cyclase → ↓ cAMP.

* Actions Of Histamine:

A) H_1-Actions:
1- Spasmogenic on Smooth muscles e.g. Bronchi, GIT & Uterus.
2- V.D. ($H_1 > H_2$) of small vessels. } Headache, Hypotension
3- ↑ Capillary permeability via } & Anaphylactic shock.
   Shrinking of endothelial cells → Exposing basement membrane → Permeable.
4- Skin → Itching, Pain & Triple response.
5- ↑ Adrenal Medulla → ↑ Release of Adrenaline.
6- *Specific H_1-Blockers* = Anti-Histaminics (See below).

B) H_2-Actions:

1- Some V.D. (V.D. is H_1 *Mainly*).
2- ↑ Heart → +ve Inotropic & Chronotropic. ↑ H.R. is due to H_2 & Reflex via ↓ Bl.p.
3- ↑ Gastric HCl secretion.
4- *Specific H_2-Blockers* e.g. Cimetidine → Treat Peptic ulcer (See GIT).

C) H_3-Actions:

1- C.N.S. → Arousal, cognition, Memory & Pathophysiology of Epilepsy.
2- Presynaptic → ↓ Release of histamine (Autoregulation) & other mediators.
3- Peripheral actions.
4- *Specific H_3-Blockers* e.g. Thioperamide & Clobenpropit.

* Therapeutic Uses of Histamine:

1-Desensitization (Obsolete).
2- Provocative Test for Paroxysmal bouts of hypertension of Pheochromocytoma.
3- Histamine aerosol → Provocative test of bronchial hyperactivity.
4-Test for gastric acidity to diagnose Achlorhydria = Pernicious anemia:
   a- Histamine alone.
   b- Histamine + H_1-Blocker (Antihistaminic) → Augmented histamine test.
   c- Betazole : A selective H_2-receptor agonist.
   d- Pentgastrin : A gastrin-receptor agonist.

* Histamine Release:

1- Drug Induced (Non-immunological): Usually basic agents → Displace histamine from tissue binding sites (No cell damage) e.g. *Morphine, d-tubocurarine, trimethaphan, atropine*, hydralazine, dextran, heparin and compound 48/80.
2- Immunological: Ag/Ab reaction on mast cells and basophils. Release by exocytosis.
3- Surface Active Agents (Surfactants): Bile salts and detergents.
4- Cell Injury: Mechanical, thermal or radiation trauma.
5- Proteolytic enzymes: Trypsin → Tissue damage
6- Venoms and Toxins.

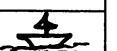
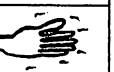
* Histamine Antagonists:

1- H_1-receptor blockers = Antihistaminics.
2- H_2-receptor blockers e.g. Cimetidine & Ranitidine (See GIT).
3- Adrenaline : A physiological antagonist.
4- ↓ Release of Histamine:
   a- Mast Cell Stabilizers e.g. Di-Na^+ Cromoglycate & Ketotifen (See Respiration).
   b- ↑ Intracellular cAMP e.g. β-Agonists (↑ A.C.) & Methyl-Xanthines (↓ P.D.E.).
5- Corticosteroids (See Hormones).
6- Histaminase (DAO) enzyme.
7- Desensitization either by histamine or better by the antigen.

Anti-Histaminics = H-1 Blockers

* Classification :

A) First Generation Anti-histaminics → Sedatives & Atropine like.

Antihistaminic	Sedation	Anti-Cholinergic	Anti-Emetic	Anti-Serotonin	Remarks
1- Dimenhydrinate *(Dramamine)*	+ + +	+ + +	+ + +	NO	Anti-motion sickness Long acting → See Sickness 
2- Diphenhydramine *(Benadryl)*	+ + +	+ + +	+ + +	+	Anti-Motion Sickness Anti-Parkinonian 
3- Promethazine *(Phenergan)*	+ + +	+ + +	+ + +	+	Sedative & Hypnotic 
4- Meclizine *(Ronin)* 5- Cyclizine *(Merazine)*	+	+	+ + +		Anti-Emetic → Teratogenic. 
6- Antazoline *(Antistine)*	+	+	±		Anti-arrhythmic. Short Acting.
7- Chlorpheneramine *(Pirafene)*	+	+ +	±		Common cold preparations. 
8- Cyproheptadine (Triactin)	+	+ +	NO	+ + +	↑ Appetite. 
9- Clemastin (Tavegyl)	±	+	NO		Long action (8-12 Hours)
10- Chemizole (Allercur)	±	+	NO		Long acting
11- Mepyramine	+	+ +	NO		Experimental

B) Second Generation Anti-histaminics

No BBB → No Sedation, No Atropine-like, No Anti-Emetic, No Anti-Serotonin & Long Duration (12 Hs)

12- Terfenadine *(Triludan)*: *Obsolete*

Cardio-Toxic Prodrug $\xrightarrow{CYP\ 450}$ Fexofenadine (Safe Active Metabolite).

13- Fexofenadine (Telfast): 60 – 180 mg od po.

Safe active carboxylated metabolite of Terfenadine.

14- *Astemizole (Hismanal)*: 5 – 10 mg od po.

15- *Mequitazine (Primalan)*: 2.5 – 5 mg bid po.

16- *Loratadine (Claritine)*: 5 – 10 mg bid po.

17- *Cetirizine (Zyrtec): 5 – 10 mg od po.*

* Chemical Classification of Antihistaminics:

1- Ethanolamines : Diphenhydramine, Dimenhydrinate & Clemastine.
2- Ethylenediamines : Antazoline & Mepyramine.
3- Alkylamines : Chlorpheneramine.
4- Phenothiazines : Promethazine
5- Piperazines : Meclizine & Cyclizine.
6- Piperidines : Terfenadine & Astemizole.

* Pharmacokinetics of Antihistaminics:

1- Absorbed orally.
2- Pass BBB *(EXCEPT* Second Generation).
   Pass placental barrier e.g. Meclizine & Cyclizine → Teratogenic.
3- Metabolized in liver: Most of them are enzyme inducers.
   Terfenadine & Astemizole (Cardio-Toxic prodrug) → Non-toxic active metabolites
4- Excreted in urine & milk → Sedate suckling baby.

* Pharmacodynamics of Anti-histaminics:

1- Competitive antagonists at H_1-receptors of histamine:
2- Block COMLETELY the Spasmogenic, ↑ Capillary permeability & Skin actions.
3- Block Most the V.D. & Hypotension.
4- NO effect on ↑ Heart or ↑ Gastric acidity.
5- *Some* have Anticholinergic = Atropine-like effect → Dry mouth.
6- *Some* have Antiserotonin effect.
7- *Some* have Na^+-Channel block = Membrane stabilizer → Local anesthetic & Direct myocardial depressant effect = Quinidine-like action e.g. Antazoline.
8- CNS *(EXCEPT Second Generation):*
   a- Mainly CNS depression → Sedation & drowsiness.
   b- Anti-emetic & Anti-motion sickness (Block H_1- & M-receptors in Vomiting center).
   c- Anti-Parkinsonism (Block of M-receptors in basal ganglia).
   d- Toxic dose → Convulsions specially in children.

* Therapeutic uses of Anti-histaminics:

1- Allergic manifestations : Conjunctivitis, rhinitis, urticaria & insect stings.
   a- In life-threatening anaphylactic shock & angio-edema → Use Adrenaline.
   b- NOT very effective in bronchial asthma:
      - Asthma is due to other mediators e.g. SRS-A & PAF.
      - Atropine-like effect → Dry bronchial secretions.
2- Motion sickness e.g. sea sickness e.g. Dimenhydrinate.
3- Vestibular disturbances (Meniere's disease) e.g. Dimenhydrinate.
4- Parkinsonism e.g. Diphenhydramine.
5- As sedative & hypnotic e.g. Promethazine.
6- Common cold e.g. Chlorpheneramine → Sedation & dries the secretions.
7- Cardiac arrhythmias e.g. Antazoline.

* Side Effects of Antihistaminics:

1- **Drowsiness** & sedation
2- **Dry mouth** & avoid in glaucoma & enlarged prostate.

} *(EXCEPT Second generation).*

3- Hypersensitivity reactions.
4- Teratogenic e.g. Meclizine & Cyclizine.
5- Toxic dose → Convulsions especially in children.
6- Enzyme inhibitors e.g. Macrolide antibiotics (Erythromycin & Clarithromycin NOT Azithromycin) & Antifungal (Ketoconazole & Teraconazole NOT Fluconazole) inhibit metabolism of Terfenadine & Astemizole (NOT Loratadine) → Cardiac arrhythmias.

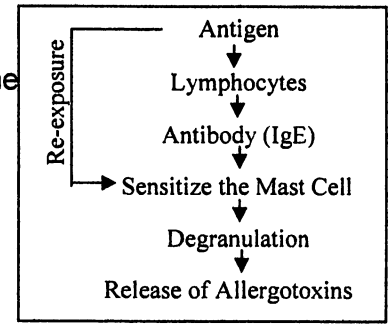
Allergy (Hypersensitivity):

1- Unpredictable abnormal response to drugs due to antigen/antibody reaction.
2- The drug itself or its metabolites may act as an antigen or a hapten.
3- Allergy: - NOT all patients - NOT all drugs - NOT first exposure
- NOT dose dependent - NOT reuse the drug again
4- Cross allergy between related drugs e.g. Penicillins & Cephalosporins.

* Types of Allergy:

A) *Type I (Immediate, Anaphylactic or IgE mediated):*

1- Antigen/Antibody (IgE) reaction on Mast cells & Basophils → Degranulation → Release of allergotoxins e.g. Histamine

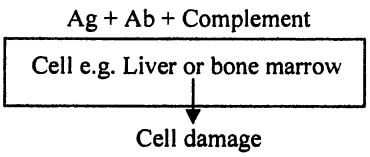


2- Manifestations: fever, rash, urticaria, photosensitivity, conjunctivitis, rhinitis, angio-edema, bronchial asthma, G.I.T. disturbances & even anaphylactic shock.

3- *Management of Type-1 Allergy:*
a- Avoid Ag if possible
b- Immunotherapy → Formation of blocking IgG.
c- Glucocorticoids e.g. Cortisol:
- ↓ Ab formation - ↓ Ag/Ab reaction - Mast cell stabilization
- ↓ PLA_2 → ↓ Arachidonic acid (PGs & LTs) & PAF formation.
- Anti-inflammatory effect on affected organs.
d- Mast cell stabilizers e.g. Cromoglycate → ↓ Release of allergotoxins.
e- Anti-histaminics e.g. Fexofenadine.
f- Adrenaline → Physiological antagonist of histamine
Life saving in severe allergy e.g. Angio-edema & Anaphylactic shock.
NB) Treatment of Anaphylactic Shock: Adrenaline + Cortisol + Anti-histaminics.

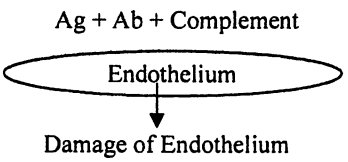
B) *Type II (Auto-allergy, Cytotoxic or Cytolytic):*

1- Antigen + Antibody (IgG & IgM) + Complement on a cell → Cell damage
2- Example: α-Methyldopa → Hepatotoxicity, hemolysis and bone marrow inhibition



C) *Type III (Arthus Reaction):*

1- Antigen + Antibody (IgG) + Complement on endothelial cell → Damage of endothelium.
2- Manifestations : Vasculitis & Serum sickness



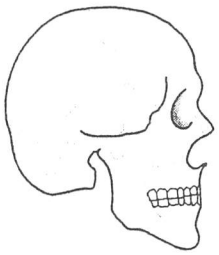
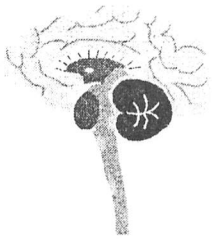
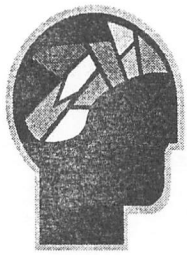
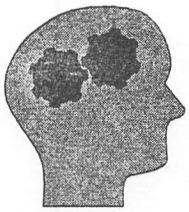
D) *Type IV (Delayed or Cell Mediated):*

1- Antigen + Sensitized T-lymphocyte → Inflammation
2- Manifestation: Contact dermatitis.

NB) Management of Types II, III & IV Allergy → Stop Ag + Cortisol

E) *Type V (Stimulatory Reaction):* Formation of LATS → Hyperthyroidism.

Central Nervous System

Chemical Warfare System

C.N.S. Depressants

Sedatives & Hypnotics (المهدئات والمنومات)

- Sedatives → Drugs that calm behavior *BUT* produces drowsiness.
- Hypnotics → Drugs that induce a state like sleep.
  Sedative-hypnotic drugs → S.D. (Sedative) & in large dose (Hypnotic).

NB) Reticular Activating System		Inhibition	Dose of S & H
1- Anxiety	→	1- Sedation	← Small
2- Alertness	→	2- Drowsiness	
3- Wakefulness	→	3- Hypnosis	← Moderate
		General anesthesia	← Large
		Coma	← Toxic
		& Death due to ↓ R.C.	← Fatal
4- Self control on	pain →	4- Hyperalgesia	
	Behavior	Delirium	

NB) Stages of Sleep:

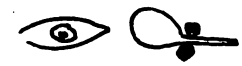
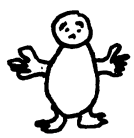
1- Non-Rapid Eye Movement (Non-REM) → Non-Dreamy sleep
2- Rapid Eye Movement (REM = Paradoxical sleep) → Dreamy sleep

NB) Characteristics of an Ideal Hypnotic:

1- Orally 2- Rapid onset 3- Adequate duration 4- Normal sleep pattern
5- No hang-over 6- No tolerance 7- No Dependence 8- No adverse effects

NB) Classification of Hypnotics:

1- Barbiturates (Bb) → Bb-GABA agonist →↓ REM, HME induction, ↓ RC & No antidote
2- Benzodiazepines (Bz) → Better than barbiturates
3- Zolpidem, Zaleplon, Zopiclone → Non-Bz → Bz-GABA agonists
4- Clomethiazole.
5- Chloral hydrate → Trichloroethanol
6- Paraldehyde → Liquid of Bad odor & taste
7- Anti-histaminics e.g. Hydroxyzine → Anti-emetic + Atropine like
8- Glutethimide → Atropine like
9- Methyprylone → Acute Porphyria
10- Ethanol → Not ethical
11- Thalidomide → Teratogenic → Phocomelia
12- Bromides → Obsolete

I- Barbiturates

1- Sedative-hypnotics Non-selective C.N.S. depressants.
2- Derivatives of Barbituric acid.
3- Barbituric acid (Malonylurea) is Not active.

* Classification & Kinetics of Barbiturates:

	Long Acting	Intermediate Acting	Short Acting	Ultra-short Acting
1- Members	Barbitone (al) Phenobarbital (one)	Amobarbital	Pentobarbital Secobarbital	Thiopentone Hexobarbitone
2- Ionization	High	Moderate	Low	Very low
3- Lipid solubility	Low	Moderate	High	Very high
4- GIT Absorption	Slow	Moderate	Rapid	Irregular
5- Passage BBB	Slow	Moderate	Rapid	Very rapid
6- Onset of action	Slow (1 – 2 hours)	Moderate (1/2-1 hour)	Rapid (1/4-1/2 hour)	Very rapid(10-20 sec)
7- Duration of action	Long (6 – 8 hours)	Moderate (4-6 hours)	Short (2 – 4 hours)	Very short(20-30 min)
8- Plasma protein	Low	Moderate	High	Very high
9- Fate	Phenobarbitone (Hepatic + Renal) Barbital (Renal Only)	Moderate hepatic metabolism	Rapid hepatic metabolism	Redistribution
10- Type of Insomnia	Patients who get up very early	Interrupted sleep	Anxious unable to start sleep	Not hypnotic I.V. anesthesia

NB) Fate of Barbiturates:

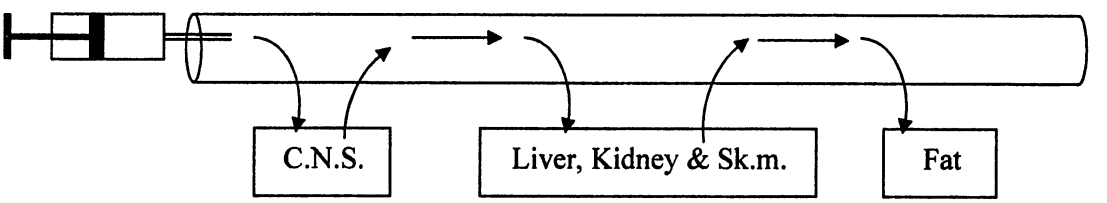
1- Phenobarbital:
   a- 25-50% Hepatic metabolism (Oxidation) by Hepatic Microsomal Enzymes.
      Repeated use → HME Induction → ↑ Own metabolism → ↓ Duration → Tolerance
   b- 50-75% Renal excretion (unchanged). Alkalinization of urine → ↑ Its excretion.

2- Barbitone → No hepatic metabolism → 100% Renal. Alkalinization → ↑ Excretion.

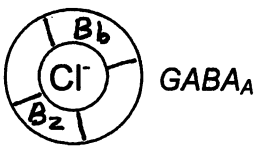
3- Amobarbital → Moderate hepatic metabolism → Oxidation.

4- Pento- & Secobarbital → Rapid hepatic metabolism → Oxidation.
   Almost No renal excretion:
   a- Highly bound to plasma proteins → Little filtration through glomeruli.
   b- High lipid solubility → Rapid reabsorption from renal tubules.

5- Thiopentone & Hexobarbitone → Redistribution from CNS to other organs.
   Repeated injection → Tissue saturation → CNS cumulation → Longer duration.



*Pharmacodynamics of Barbiturates:



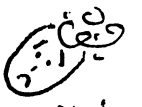
$GABA_A$

1- C.N.S.:

- **Mechanism of Action of Barbiturates:**

1- They stimulate specific Barbiturate receptor → GABA-mimetic & facilitate GABA-A transmission → ↑ Cl^- influx → Hyperpolarization → Post-synaptic inhibition.
2- Reversible CNS depression in a descending manner.
3- Affect mainly the Cortex & Reticular Activating System.
4- They can produce any degree of CNS inhibition (Mild sedation → Coma & death).

- **Actions of Barbiturates:**



1- Sedative action *BUT* → Drowsiness. هادي بس مدروخ
2- Hypnotic action *BUT* Abnormal sleep → ↓ REM: نوم بدون أحلام ويصحى مقريف
   a- Hang-over.
   b- Rebound paradoxical sleep after tolerance or stopping the drug.
3- Amnesia.
4- General anesthesia, especially Ultra-0short acting barbiturates.
5- Anti-Convulsant (ALL barbiturates treat ALL convulsions)
   Anti-Epileptic (Phenobarbital treats Grand Mal & worsens Petit mal epilepsy).
6- Potentiate analgesics.
   But, if used alone in presence of pain → Hyperalgesia & delirium.
7- Large Dose → ↓ Vital medullary centers:
   a- ↓ R.C.: ↓ Its sensitivity to CO_2 → Hypoventilation & Hypoxia.
   b- ↓ V.M.C. → Hypotension.
   c- Heat Regulating Center (HRC) → Hypothermia.

2- C.V.S.:

1- Therapeutic Dose → Minimal effect.
2- Large dose → Hypotension (↓ V.M.C., ↓ Heart & V.D.).

3- Respiratory → Hypoventilation & Hypoxia.

4- G.I.T. → Hypomotility & Hyposecretion.

5- Kidney → Oliguria (↓ Bl.p. & ↑ A.D.H.).

6- Hormones → ↑ A.D.H. & ↓ A.C.T.H.

7- Uterus:

1- Large dose → ↓ Uterine contractility → Post-partum hemorrhage.
2- Pass placental barrier → Neonatal asphyxia.

8- Sk.m. → Large dose → Mild relaxation.

9- Liver → Hepatic Microsomal Enzyme Inducer:

1- ↑ Own metabolism → Tolerance & Cross-tolerance.
2- ↑ Metabolism of other drugs → Drug interactions.

*Therapeutic Uses of Barbiturates:

1- ***Sedative*** to alleviate anxiety, nervous tension & irritability.
2- ***Hypnotic*** to treat insomnia:
   a- Short acting (Pento & Seco) → Shorten sleep latency → Useful to initiate sleep.
   b- Intermediate acting (Amo) & long acting (Pheno) → Useful to maintain sleep.
3- Psycho-***analysis*** & Narco-analysis.
4- ***Pre-anesthetic*** medication.
5- ***I.V. Anesthesia*** (Ultra-short acting).
6- ***Counteract*** C.N.S. stimulant drugs e.g. Local anesthetics & Ephedrine.
7- ***Anti-convulsant*** e.g. Thiopentone in Febrile convulsions.
   Anti-Epileptic: Phenobarbitone in Grand mal epilepsy & Status epilepticus.
8- ***Hyperbilirubinemia*** & Kern-ictrus: Phenobarbital → Enzyme induction → ↑ Metabolism of bilirubin.

*Adverse Effects of Barbiturates:

1- Idiosyncrasy → ***Acute Porphyria*** in patients with Acute Intermittent Porphyria.
   Barbiturates → Induction of Dela-Amino-Laevulinic Acid Synthetase enzyme.

ALA-Synthetase — *Normally Strong Enzymes*

Protoporphyrine ⟶ Porphyrine ⟶ Haem

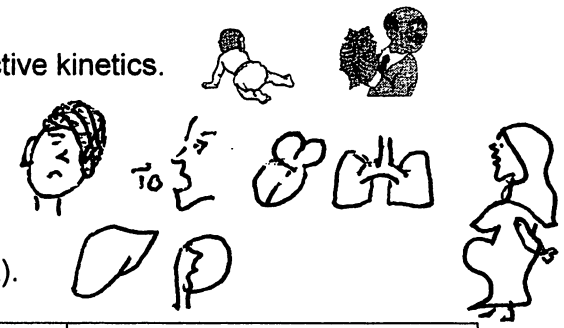
Barbiturates +++ — *(TOXIC)* — *Abnormally weak enzymes*

2- Idiosyncrasy → Excitation.
3- Induction of H.M.E. → Tolerance, Cross tolerance, Dependence & Drug Interactions.
4- Drug Interactions:
   a- ***Hepatic Microsomal Enzyme Induction*** → ↑ Metabolism of Other drugs e.g. Oral anticoagulants, hypoglycemics & contraceptives.
   b- Barbiturates + Ethyl alcohol → Synergism → Severe ↓ C.N.S.
   c- Barbiturates + Aspirin → Potentiation.
   d- Barbiturates + Caffeine → Physiological antagonism.

5- Allergy.
6- Abnormal Sleep → ↓ R.E.M. → Hang-over & Rebound paradoxical sleep.
7- Amnesia & Automatism.
8- Acute Poisoning:
   Coma, Hypoventillation, Hypoxia, Hypotension, Hypothermia → Death due to Respiratory failure (↓ R.C.).
   *Management Of Acute Poisoning:
   a- Endotrachial intubation + Artificial respiration.
   b- Stomach wash → If taken orally & No coma to avoid aspiration pneumonia.
   c- Promote urinary excretion of Long Acting Barbiturates:
      - Alkalinization of urine (I.V. $NaHCO_3$).
      - I.V. fluids + Diuretics (Frusemide or Mannitol).
      - Hemodialysis.
   d- Analeptics may be used e.g. Doxapram I.V. infusion.
   e- Antibiotics to guard against aspiration pneumonia.
9- Addiction: Long use of barbiturates → Tolerance → Dependence → Addiction.
   Sudden stop → Withdrawal manifestation → Reversal → Excitation & even convulsions
   Management by gradual withdrawal of barbiturates + Psychotherapy.

*Contraindications of Barbiturates:

1- Allergy to barbiturates.
2- Idiosyncrasy (Acute Intermittent Porphyria).
3- Extremities of age → Pediatrics & Geriatrics → Defective kinetics.
4- Head injury → More ↓ R.C.
5- Alone in pain → Hyperalgesia.
6- Shock → More ↓ Bl.p. & ↓ Tissue perfusion.
7- Respiratory diseases e.g. Acute bronchial asthma.
8- Liver & Kidney disease → Defective kinetics.
9- Pregnancy (Addict baby) & Labor (Neonatal asphyxia).



	Barbiturates	Benzodiazepines
1- Sleep pattern:	1- Marked ↓↓ R.E.M.: a- Hang-over b- Rebound paradoxical sleep	1- Less ↓ R.E.M.: a- Less b- Less
2- H.M.E.:	2- Induction: a- Tolerance & Cross tolerance b- Dependence c- Drug interactions.	2- No induction: a- Less b- Less c- Less
3- Therapeutic index:	3- Low (↓ R.C.)	4- High (safer on R.C.)
4- Specific Antidote:	4- No	5- Flumazenil

2- Benzodiazepines (Bz)

* Classification:

A) *Long Acting* : **Flurazepam** *(Dalmane)* **& Nitrazepam** *(Mogadon)*

1- Flurazepam (Active, t1/2=2 hs) → Active Metabolite (Norflurazepam), t1/2=70 Hs.
Nitrazepam (Active, t1/2 = 26 hr) → Inactive metabolite.
2- Both produce day time sedation & drowsiness. Repeated use → Cumulation → Side effects.
3- Taken orally when needed. Dose: 15-30 mg at bed time Orally.

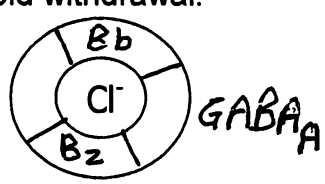
B) *Intermediate Acting* : **Temazepam** *(Normison)*

1- Temazepam (Active, t1/2 = 12 Hs) → Inactive metabolite.
2- Slowly absorbed → Delayed onset → Not useful to initiate sleep *But* to maintain it.
3- Dose : 15-30 mg at bed time Orally.

C) *Short Acting* : **Triazolam** *(Halicon)*

1- Triazolam (Active, t1/2 = 2 Hs) → Active metabolite (Hydroxytriazolam), t1/2 = 2 Hs.
2- Rapid oral absorption → Rapid onset → Useful to initiate sleep.
3- Rapid metabolism → Short duration → Not used to maintain sleep.
No day time sedation *But* may cause day-time anxiety due to rapid withdrawal.
4- Dose : 0.125 - 0.25 mg at bed time Orally.

* Mechanism of Action of Bz :



1- Bz stimulate specific Bz-receptor → Facilitate $GABA_A$ transmission →
↑ Cl^- influx → Hyperpolarization → Post-Synaptic Inhibition of neurons.
2- Benzodiazepine receptors are of ***TWO types Bz_1 & Bz_2 (Omega ω_1 & ω_2)***.

* Advantages of Bz as Hypnotics :

1- Less ↓ of REM → Less hangover & Less rebound paradoxical sleep.
2- NO Hepatic Microsomal Enzyme Induction → Less tolerance, Less dependence and Less drug interactions.
3- Wide safety margin → Safer than barbiturates on R.C. & C.V.S.
4- Available specific antidote = **Flumazenil**.

* Adverse Effects of Bz:

1- Dependence → Addiction. Sudden withdrawal → Anxiety & convulsions.
2- Daytime sedation after long acting Bz or Anxiety after short acting Bz.
3- Affect mental. Psycho-motor & Sexual functions.
4- **Amnesia** (specially Triazolam).
5- Aged patients → Mental confusion & hypotension.
6- Additive to Alcohol → Severe CNS ↓.
7- Ataxia.
8- Amenorrhea, ↓ Ovulation, ↓ Ejaculation & Teratogenic.
9- ↑ Appetite → ↑ Body weight.
10- Allergy.
11- Acute toxicity: Rare unless if used with alcohol → ↓ CNS, CVS & Respiration.
Treatment of Toxicity → **Flumazenil** + Supportive treatment.

NB) **Flumazenil** *(Anexate) :*
1- Selective and competitive block of Bz-receptors → Antagonizes ALL actions of Bz whether therapeutic or toxic. It has no effect on other CNS ↓ eg Barbiturates.
2- Extensive (80%) hepatic first pass metabolism, so used IV (0.3 -1 mg).
3- Short $t_{1/2}$ = 1 hour, so used by repeated IV injections or IV infusion.

3- *Non-Benzodiazepines Bz-GABA Agonists*

1- Zopiclone: No advantage over Bz.

2- Zolpidem *(Stilnox, 10 mg)*:
a- Non-benzodiazepine.
b- Selective Bz_1 (ω_1) receptor agonist. Can be antagonized by flumazenil.
c- Hypnotic with minimal ↓ REM → Minimal hangover
d- Minimal muscle relaxation or anticonvulsant.
e- Minimal tolerance & dependence.
f- Short acting ($t_{1/2}$ = 2 hrs) → Day time anxiety.

3- Zaleplon Similar to Zolpidem *BUT* short $t_{1/2}$ = 1 hour.

4- *Clomethiazole*

1- GABA-A Agonist → Hypnotic & Anti-convulsant.
2- Short $t_{1/2}$ = 4 hours.
3- Adverse effects: Dependence & Narrow safety margin → ↓ R.C.

5- *Chloral Hydrate*

*** Kinetics:**

1- Absorbed Orally & Rectally.

2- Fate:

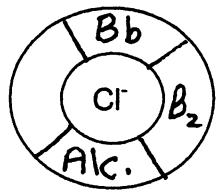
a- Chloral Hydrate —*Alcohol Dehydrogenase (RBCs, Liver & Kidney)*→ *Active Trichloroethanol*

b- Trichloroethanol ↘ Oxidation → Inactive Trichloroacetic acid.
Conjugation with Glucuronic acid → Inactive Urochloralic acid.

c- Excretion in urine.

*** Dynamics → *Hypnotic effect*:**

1- Onset (1/4-1/2 Hour) & Duration (6-8 Hours):
2- Therapeutic doses → Safe on C.V.S. & R.C.
3- Bad taste & Irritant → Dilute with milk or fruit juice.
4- Abnormal sleep pattern → Some hang-over.
5- Hepatic microsomal enzyme induction.



GABA$_A$

*** Therapeutic Use → *Hypnotic*** (½-1 g diluted with milk or fruit juice) in patients who can not tolerate barbiturates e.g. extremities of age (***Geriatrics & Pediatrics***).

*** Contraindications:**

1- Gastritis, peptic ulcer & proctitis. 2- Advanced liver & kidney diseases.
3- Chloral hydrate + Alcohol → Synergism → Severe C.N.S. ↓ → Come & ↓ R.C.

*** Toxicity:**

1- Acute → Coma, ↓ R.C., ↓ V.M.C. & Pin Point Pupil.
May be mistaken for Morphine poisoning. Use Naloxone to differentiate.
2- Chronic → Tolerance & Dependence. 3- May be carcinogenic.

6- *Paraldehyde:*

Liquid of bad odor & bad taste.

*** Actions & Uses:**

1- *Orally* (*5ml* added to fruit juice or milk) → **Hypnotic**:
a- Rapid acting (within 10-15 minutes) & Adequate duration (6-8 hours).
b- NOT followed by hangover.
c- Safe on respiration & circulation when used in therapeutic doses.
2- *IM 10 ml* → **Anticonvulsant** (↓ Both mono & polysynaptic pathways) → Useful in Status epilepticus
3- *Rectally 50 ml* as retention enema → **Basal** anesthesia & **pre-anesthetic** medication.

*** Disadvantages:**

1- Bad odor & bad taste. 2- Tolerance & habituation.
3- Not analgesic. If used alone in pain → Excitation.
4- Contraindicated in G.I.T., liver & lung diseases.

8- *Anti-histaminics:*

1- **Examples**: Hydroxyzine (Atarax), Diphenhydramine & Promethazine.
2- **Actions**: Sedative-hypnotic, Antihistaminic, Anticholinergic & Antiemetic.
3- No drug dependence.

9- Ethyl Alcohol (Ethanol):

* Pharmacokinetics:

1- Well absorbed orally from stomach & intestine. Presence of food delays absorption.
2- Distributed allover the body fluids.
3- 95% Metabolized by all tissues specially the liver, about 10 ml/hour = ***Zero-order kinetics***:
   a- Ethanol $\xrightarrow{\text{Alcohol Dehydrogenase}}$ Acetaldehyde $\xrightarrow{\text{Aldehyde Dehydrogenase}}$ Acetic acid $\rightarrow CO_2 + H_2O + E.$
   b- Pyridoxine (Vit B-6) & Fructose (Levulose) $\rightarrow \uparrow$ Metabolism of alcohol.
   c- Chlorpromazine & Ethacrynic acid $\rightarrow \downarrow$ Alcohol dehydrogenase $\rightarrow \uparrow$ Blood level of alcohol $\rightarrow$ Alcohol intolerance.
   d- ***Disulfiram, Citrated Calcium Carbamide (CCC)***, Metronidazole, Some Cephalosporins & Sulphonylureas $\rightarrow \downarrow$ Aldehyde dehydrogenase $\rightarrow \uparrow$ Acetaldehyde $\rightarrow$ Unpleasant symptoms.
4- 5% Excreted unchanged in breath & urine.

* Pharmacodynamics:

A) Local actions & Uses:

1- ***Astringent*** by precipitation of surface proteins $\rightarrow$ *Useful to harden the skin in bed sores.*
2- ***Antiseptic*** in 70% concentration $\rightarrow$ *Useful as Antiseptic.*
3- ***Irritant*** $\rightarrow$Mucous membrane, denuded surface & S.C. $\rightarrow$ *Useful as Reflex Analeptic.*
4- ***Local Anesthetic*** if injected near nerve $\rightarrow$ *Useful in Trigeminal neuralgia.*
5- ***Cooling*** effect by rapid evaporation $\rightarrow$ *Useful as Cooling fomentations.*
6- ***Rubeficient*** on skin $\rightarrow$ *Useful with Counterirritants e.g. in arthritis.*

B) Systemic Actions Of Ethyl Alcohol:

1- C. N. S.:

a- $\uparrow$ GABA-A transmission $\rightarrow \uparrow Cl^-$ Influx $\rightarrow$ Hyperpolarization $\rightarrow$ Postsynaptic inhibition.
b- General CNS depressant $\rightarrow$ Sedation, hypnosis & general anesthesia ***BUT*** narrow safety margin $\rightarrow \downarrow$ R.C.
c- Analgesic.
d- $\downarrow$ Self restraint $\rightarrow$ Euphoria, overconfidence, uncontrolled speech & emotions.
e- $\downarrow$ Acuity of sensations & $\downarrow$ Muscle coordination $\rightarrow$ Staggering gate.
f- $\downarrow$ Mental & physical efficacy & $\uparrow$ Reaction time $\rightarrow$ Accidents e.g. motorcar.

2- Hyptheramia: $\downarrow$ V.M.C., $\downarrow$ H.R.C. & Direct VD $\rightarrow$ Skin VD $\rightarrow \uparrow$ Heat loss $\rightarrow$ Sense of warmth ***BUT*** $\downarrow$ Body Temperature.

3- C. V. S.:

a- Skin V.D. $\rightarrow$ Flushing & sense of warmth.
b- Relief anginal pain by its analgesic effect ***BUT NOT*** correct cardiac ischemia.

4- G. I. T.:

a- Stomachic & Carminative.
b- Up to 10% conc. $\rightarrow \uparrow$ Gastric secretions (Acid NOT pepsin).
c- Concentrations > 20% $\rightarrow \downarrow$ Gastric secretions.
d- Concentrations > 40% $\rightarrow$ Gastritis.
e- Chronic alcoholism $\rightarrow$ Chronic gastritis, achlorhydria, Fatty infiltration & cirrhosis of liver.

5- Kidney: Diuresis due to $\downarrow$ A.D.H.

6- Endocrine: $\uparrow$ ACTH, $\downarrow$ ADH & $\downarrow$ Oxytocin $\rightarrow$ Delay labor.

NB) *Tolerance to Alcohol* $\rightarrow$ Acquired tolerance Mainly to CNS action But Not to diuresis.

* Toxicity To Ethanol:

A) Acute Toxicity:

1- Manifestations:

a- Euphoria, overconfidence, slurred speech, staggering gate, blurring of vision & hiccup.
b- Hypothermia, tachycardia, slow respiration with alcohol smell & vomiting.
c- Hypoglycemia, ↑ Intracranial pressure.
d- Coma & Death due to respiratory failure.

2- Management;

a- Keep the patient warm b- Artificial respiration c- Stomach wash
d- If Drowsy → Use Caffeine e- If Excited → Use Diazepam
f- Hypertonic glucose solution to relief ↑ I.C.P. & brain edema.
g- Pyridoxine (100 mg I.V.) + Fructose (PO or I.V.) → Speed metabolism of Alcohol.

B) Chronic Alcoholism;

1- Manifestations:

a- Dependence → Tolerance, cross tolerance with Bb, Bz & anesthesia → ***ADDICTION***.
b- Devitalization of almost ALL organs specially Liver cirrhosis.
c- Deterioration of mental capacity & moral sense.
d- Delirium tremens → Hallucinations, excitations & tremors.
e- Deficiency of Thiamin → Neuritis.
f- Decreased immunity.
g- ***Fetal Alcohol Syndrome (FAS)*** → Microcephaly & mental retardation.

2- Management:

1- Psychological & Nutritional support (Vit B-complex specially Thiamin).
2- Gradual withdrawal of alcohol & substitution with long acting Bz e.g. Diazepam.
3- ***Disulfiram*** (acts for 6-12 days) or ***Citrated Calcium Carbamide*** (**C.C.C.**, acts for 8-12 hours & better tolerated) → They ↓ Aldehyde dehydrogenase. If patient ingest alcohol → Accumulation of Acetaldehyde → Headache, flush, nausea, palpitations & dyspnea → Help the patient to quit drinking.

Hallucinogenic (Psychotogenic) Agents

1- Cannabis (Hashish, Bango, Kif, Marijuana):

1- Active principle is Tetra-hydro-cannabinol → ↑ Specific cannabinoid receptors.
2- Cannabinoid receptors are present mainly in CNS & in lymphoid system.
3- ***Anandamide*** is an endogenous ligand for the cannabinoid receptors in CNS
2- The person loses the sense of time & space.
3- Euphoria & attacks of uncontrolled laughter.
4- Congestion of conjunctiva, ↓ I.O.P. & Tachycardia.
5- Derivatives are used clinically as analgesics & Antiemetics e.g. ***Nabilone***.

2- Lysergic Acid Di-Ethylamide (LSD, Acid);

Related to Ergot alkaloids. Central 5-HT Agonist (Auto-receptors) ***BUT*** peripheral 5-HT antagonist.

3- Mescaline: Obtained from Mexican cactus. Cross tolerance with LSD.

4- Khat (القات)→ Amphetamine-like

3- Phencyclidine (PCP, Angle Dust) :

a- Related chemically to Meperidine (Opioid) & Ketamine (IV Anesthesia).
b- It Stimulates σ-opioid receptor & blocks NMDA-glutamate receptor.
c- Produces Dissociative Anesthesia = Analgesia, stupor & Amnesia. Patient is conscious but detached from the environment.

Psychotropic (Psychoactive) Drugs

Drugs that affect behavior and psychology of individuals.

*** *Classification of Psychotropic Drugs:***

A) Tranquilizers (Psycholeptics):

1- Minor Tranquillizers (Anti-anxiety , Anxiolytics): e.g. Diazepam.
2- Major Tranquillizers (Anti-psychotic , Neuroleptics): e.g. Chlorpromazine.

B) Anti-Depressants and Lithium:

1- Anti-Depressants (Mood Elevating): e.g. Tricyclic antidepressants.
2- Lithium Carbonate (Anti-Manic & Mood Stabilizing).

C) Psychomotor Stimulants e.g. Amphetamine.

D) Psychotomimetics (Psychodysleptics , Hallucinogens). e.g. LSD.

Minor Tranquillizers (Anxiolytic, Anti-Anxiety)

Drugs used in treatment of anxiety and nervous tension.

*** *Classification:***

1- Benzodiazepines	e.g. Diazepam.
2- 5-HT Agonists	e.g. Buspirone, Ipsapirone & Gepirone.
3- β-Blockers	e.g. Propranolol.
4- Miscellaneous	e.g. Meprobamate.

I- Benzodiazepines (Bz)

* Pharmacokinetics of Bz:

A) Absorption:

1- Well absorbed orally mostly from the duodenum:

Clorazepate (Inactive, Prodrug) —*Decarboxylated by Gastric HCl*→ Active Metabolite
→ Desmethyldiazepam = Nordiazepam → Rapidly absorbed.

2- I.M. injection
   a- *Most* Bz have *erratic* absorption due to binding to sk.m. proteins.
   b- *Lorazepam* is well absorbed, so useful in status epilepticus when IV is difficult.
3- I.V. injection e.g. Diazepam in status epilepticus or as I.V. anesthesia.

B) Distribution:

1- All over the body and pass BBB and placental barriers.
2- Highly bound to plasma proteins (70-99%).

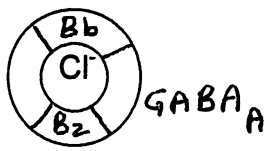
C) Metabolism:

1- Mainly by Hepatic Microsomal Enzymes:
   a- Oxidation (Usually → Activation)
   b- Conjugation with glucuronic acid (Always Inactivation).
2- Bz Activated in liver → Diazepam, Chlordiazepoxide & Alprazolam.
   Bz Inactivated in liver → Lorazepam & Oxazepam.

D) Excretion: Renal excretion of the inactive hydrophilic metabolites.

* *Mechanism of Action of Bz:*

1- They bind with specific Bz (Bz_1 & Bz_2 = ω_1 & ω_2) receptors → Activate $GABA_A$ transmission →↑ Cl^- Influx → Hyperpolarization → Postsynaptic inhibition.
2- Some Bz may act as Agonists, Partial agonists or Inverse agonists → Reverse actions → Anxiety & convulsions.



* *Pharmacological Actions of Bz.*

1- Anxiolytic (Anti-Anxiety):

a- An action on the Limbic system.
b- This action is usually accompanied by a Sedative Effect.
b- On animals → Taming effect.
c- *Examples*:
   - Bz with Long $t_{1/2}$ > 24 hours : Diazepam, Chlordiazepoxide & Clorazepate.
   - Bz with Medium $t_{1/2}$ = 6-12 hours: Oxazepam, Lorazepam and Alprazolam.

2- Hypnotic Effects:

a- An action on Reticular formation.
b- Advantages over Barbiturates:
   - Less ↓ of REM → Less hangover & Less rebound paradoxical sleep.
   - NO Hepatic Microsomal Enzyme Induction → Less tolerance, Less dependence and Less drug interactions.
   - Wide safety margin → Safer than barbiturates on R.C. & C.V.S.
c- *Examples*:
   - Long Acting: Flurazepam & Nitrazepam.
   - Medium Acting: Temazepam.
   - Short Acting: Triazolam.

3- Amnesia especially after Triazolam (due to sedative effect).

4- IV Anesthesia:

1- Diazepam → Induction and Basal anesthesia (10-40 mg SLOW IV).
2- Midazolam is better → Quicker, shorter & less irritant.
3- Irritant → Pain and thrombophlebitis.

5- Skeletal Muscle Relaxant:

1- Inhibit *BOTH* polysynaptic & monosynaptic pathways.
2- *Examples*: Diazepam & Clonazepam.

6- Anticonvulsant & Antiepileptic effect:

1- Diazepam 1 mg Slow I.V. → Drug of Choice in Status Epilepticus.
2- Clonazepam:
   a- Orally → Broad spectrum Anti-Epileptic → Useful in Grand Mal, Petit Mal & Partial seizures.
   b- 10 mg Slow I.V. → Effective is Status Epileptics.

7- Alprazolam has an Anti-depressant effect.

8- **NO** C.V.S. or Respiratory depressant effects if used in therapeutic doses.

9- **NO** Hepatic microsomal enzyme induction.

10- **NO** Autonomic or Extra-pyramidal manifestations (Unlike Major Tranquilizers).

* *Tolerance & Physical Dependence:*

1- Long use of Bz more than a week results in tolerance mainly to the sedative effect. Little tolerance to the anxiolytic effect.
2- Psychic and Physical dependence occur after long use. Sudden withdrawal of Bz → Abstinence (Withdrawal) syndrome → Anxiety & Convulsions.
3- There is cross-tolerance and cross-dependence between Bz, Bb and Ethanol.

* *Therapeutic Uses of Bz:*

1- Anxiety.
2- Insomnia:
   a- Initiate sleep by Triazolam.
   b- Maintain sleep by Temazepam or Flurazepam.
3- Preanesthetic medication e.g. Diazepam.
4- I.V. Anesthesia: Diazepam & Midazolam.
5- Anti-Spasticity agent for Sk.m. spasm e.g. Diazepam & Clonazepam.
6- Anti-Convulsant & Anti-Epileptic:
   a- SLOW I.V. Diazepam & Clonazepam in Status epilepticus.
   b- Oral Clonazepam is a broad spectrum anti-epileptic.
7- Alprazolam in Anxiety, Psychic depression, Panic & Phobic disorders
8- Alcohol withdrawal:
   a- Cross dependence between Bz and alcohol.
   b- Use long $t_{1/2}$ Bz e.g. diazepam.
9- Diagnostic aids in psychiatry and neurology.

* *Adverse Effects of Bz:*

1- Dependence → Addiction. Sudden withdrawal → Anxiety & convulsions.
2- Daytime sedation after long acting Bz or Anxiety after short acting Bz.
3- Affect mental. Psycho-motor & Sexual functions.
4- **Amnesia** (specially Triazolam).
5- Aged patients → Mental confusion & hypotension.
6- Additive to Alcohol → Severe CNS ↓.
7- Ataxia.
8- Amenorrhea, ↓ Ovulation, ↓ Ejaculation & Teratogenic.
9- ↑ Appetite → ↑ Body weight.
10- Allergy.
11- Acute toxicity: Rare unless if used with alcohol → ↓ CNS, CVS & Respiration.
Treatment of Toxicity → **Flumazenil** + Supportive treatment.

NB) **Flumazenil** *(Anexate) :*
1- Selective and competitive block of Bz-receptors → Antagonizes ALL actions of Bz whether therapeutic or toxic. It has no effect on other CNS ↓ eg Barbiturates.
2- Extensive (80%) hepatic first pass metabolism, so used IV (0.3 -1 mg).
3- Short $t_{1/2}$ = 1 hour, so used by repeated IV injections or IV infusion.

* *Classifications of Bz:*

A) According to t1/2:

1- Long Acting Bz → t1/2 > 24 hours → Diazepam, Chlordiazepoxide, Clorazepate, Flurazepam & Nitrazepam.
2- Intermediate Acting Bz → t1/2 = 6-12 hours → Alprazolam, Lorazepam, Oxazepam & Temazepam.
3- Short Acting Bz → t1/2 < 6 hours → Midazolam & Triazolam.

B) According To Activation/Inactivation in Body:

1- Bz ***Inactivated*** in Body → Nitrazepam, Temazepam, Oxazepam, Clonazepam & Lorazepam.
2- Bz ***Activated*** in Body:
   a- Activation in Stomach → Clorazepate.
   b- Hepatic Activation: Alprazolam, Diazepam, Midazolam, Flurazepam, Triazolam & Chlordiazepoxide.

II- Buspirone "BuSpar":

1- Partial agonist on presynaptic 5-HT_{1A}-receptor.
2- ***Anxio-selective***, with minimal sedation → It does not affect driving skills.
It has no hypnotic, muscle relaxant or anti-epileptic effects.
3- *Little* dependence, least additive to alcohol and **NO** cross-tolerance or cross-dependence with other sedative hypnotics e.g. Bb or Bz.
4- Its anxiolytic effect *appears after 1-2 weeks*.
Effective in *generalized anxiety syndrome* when delayed onset is accepted.
5- *Metabolized* in liver into active metabolites → α_2-blocker.
6- *Side effects* → Nervousness, tachycardia & GIT distress.
7- *Drug interaction* with MAO.I.

III- Propranolol "Inderal":

1- Non-selective β-receptor blocker.
2- Treats *BOTH* Psychic & Somatic (Sympathetic) components of anxiety.
3- Useful specially in situational Panic & Phobic disorders e.g. Car driving in busy traffic, public speaking, playing musical instrument, surgery, some sports that need calm skill e.g. bowling and shooting, and examinations sittings.

IV- Meprobamate (Miltown, Equanil)

1- *Propanediol* derivative related to *Mephenesine* (A central muscle relaxant).
2- Its Pharmacology → Similar to Bz.

Major Tranquillizers
(Anti-Psychotic , Neuroleptics, Anti-Schizophrenic)

Useful in major psychiatric illness e.g. Schizophrenia and Mania.

* *Classification of Anti-Psychotic Drugs:*

1- Phenothiazines:
a- *Aliphatic Side Chain*: Chlorpromazine.
b- *Piperidine Side Chain*: Thioridazine & Mesoridazine.
c- Piperazine Side Chain: Trifluperazine, Fluphenazine & Perphenazine.

2- Thioxanthenes:
a- *Aliphatic Side Chain*: Chlorprothixene.
b- *Piperazine Side Chain*: Zuclopenthixol, Flupenthixol & Thiothixene.

3- Butyrophenones: Haloperidol & Droperidol.

4- *Miscellaneous (Atypical) Antipsychotic Drugs*:
a- Pimozide b- Sulpride
c- Clozapine d- Risperidone e- Olanzepine

NB) Most of the neuroleptics act via blocking central D_2-receptors in hypothalamus and limbic system.

N.B.) ***Dopamine receptors*** :

1- D_1-Family (D_1 + D_5) → ↑ G_s → ↑ Adenylate Cyclase → ↑ cAMP → Most of peripheral actions e.g. Renal VD.
2- D_2-Family (D_2 + D_3 + D_4) → ↑ G_i → ↓ Adenylate Cyclase → ↓ cAMP, ↑ K^+ & ↓ Ca^{2+} → Most of Central actions e.g. Psychotic & Anti-Parkinsonian actions.

Site	Dopamine	Dopamine Antagonists
1- Limbic system, Frontal cortex & Hypothalamus.	1- Euphoria then Psychosis	1- Anti-Psychotic.
2- Basal Ganglia.	2- Anti-Parkinsonian.	2- Parkinsonism.
3- Hypothalamus.	3- ↑ Temperature ↓ Appetite ↓ Prolactin	3- ↓ Temperature → Hypothermia ↑ Appetite ↑ Prolactin
4- C. T. Z.	4- Nausea & Vomiting	4- Anti-emetic EXCEPT in motion sickness

All Vomiting → ↑ CTZ (D_2-receptor) → ↑ Vomiting Center (M-receptor) → Vomiting.
Motion Sickness → ↑ CTZ
Neuroleptics → ↑ CTZ
Hyoscine → ↑ Vomiting Center

Chlorpromazine *(Largactil)*

* *Pharmacodynamics*:

1- C. N. S. :

a- Anti-Psychotic → Blocks Dopamine (D_2-receptor) in limbic system, Neocortex & Hypothalamus.
b- Basal Ganglia → Large doses → Block D_2-receptors → Worsen Parkinsonism.
c- Hypothalamus:
- Hypothermia → ↑ Heat loss by cutaneous VD (↓ HRC, ↓ VMC & α-Blocker)
↓ Heat production by ↓ shivering.
- ↑ Appetite & Weight gain.
- ↑ Prolactin.

d- ↓ C.T.Z. : Antiemetic in ALL vomiting EXCEPT in motion sickness.
e- Potentiates other CNS depressants e.g. Barbiturates & Morphine.
f- Lowers seizure threshold.

2- Endocrines:

a- ↓ ACTH b- ↓ Growth hormone. c- ↑ MSH.
d- ↓ FSH & ↓ LH gonadotrophins → Infertility & Amenorrhea in females.
e- ↑ Prolactin → Gynecomastia & Galactorrhea (Non-puerperal lactation).

3- *Receptors*:

a- Potent Anti-Dopamine.
b- Potent α-blocker.
c- Weak Anti-Muscarinic (Atropine-like).
d- Weak ganglion blocker.
e- Potent Anti-Serotonin.
f- Weak H_1-blocker (Anti-Histamine)

4- *Skeletal Muscle* → Curare like → Muscle relaxation.

5- *Local Anesthetic.*

6- *C. V. S.*:

a- Hypotension & Postural Hypotension → ↓ VMC + Ganglion Block + α-Block + Direct VD + Direct myocardial depressant.
b- Tachycardia → Atropine like + Reflex from ↓ Bl.p.
c- Increases coronary flow.

* Therapeutic Uses:

1- *Psychosis* e.g. Schizophrenia (200-1000 mg/Day). Treats mainly the positive signs such as hallucinations, illusions & delusions.
2- *Preanesthetic* medication.
3- *Hypothermic* agent → ↓ Tissue metabolism during cardio-pulmonary surgery.
4- *Hiccough.*
5- *Anti-emetic* (25 mg) EXCEPT motion sickness & pregnancy (Teratogenic).
6- *Anti-pruretic* = *Treat itching.*

* Drug Interactions of Chlorpromazine:

1- Chlorpromazine *Potentiates*
   a- Sedatives e.g. Alcohol.
   b- Hypotensives e.g. V.D.
   c- Anti-cholinergics e.g. Atropine
   d- Muscle relaxants e.g. Curare
3- It ↓ Neuronal uptake$_1$ of Guanethidine → Antagonize its hypotensive effect.
4- Chlorpromazine → α-blocker → Reverses pressor effect of Adrenaline.

* Side Effects of Chlorpromazine:

1- C.N.S.:

a- S E D A T I O N.
b- *Extrapyramidal Manifestations*:
   Treat by ↓ dose of neuroleptic & use Anti-cholinergic Anti-Parkinsonian drug.
   1- Acute dystonia (muscle spasm).
   2- Akathisia (motor restlessness).
   3- Parkinsonism.
c- *Neurolept-malignant syndrome* (NMS). Idiosyncratic reaction, similar to Malignant Hyperthermia. Treat by IV Dantrolene or Bromocriptine.
d- *Tardive dyskinesia* (abnormal movements) occurs after long use of neuroleptics, due to upregulation of D-receptors. NO treatment. Can be prevented by lithium.

2- Increased body weight.
3- Opacities of cornea and lens.
4- Dry mouth
5- Allergy : Dermatitis, photosensitivity & Agranulocytosis.
6- Tachycardia.
7- Endocrine disturbances e.g. Gynecomastia & galactorrhea.
8- Allergic obstructive cholestatic jaundice.
9- Teratogenic, so not used in vomiting of pregnancy.
10- Postural hypotension.

Other Major Tranquilizers

1- Thioridazine (*Melleril*):

1- Phenothiazine, similar to chlorpromazine, BUT:
   a- NOT Anti-emetic.
   b- RARE Extra-pyramidal manifestations.
2- Uses : Schizophrenia & Premature ejaculation in males (α_1-block).
3- Side Effects : Similar to Chlorpromazine + Cardiotoxic & Retinopathy.

2- Trifluperazine (*Stelazine*) :

Phenothiazine, similar to chlorpromazine, BUT: More D_2-Block → More POWERFUL Anti-psychotic & More Extrapyramidal manifestations.

3- Thioxanthenes:

1- *Examples*:
   a- **Chlorprothixene** (*Taractan).*
   b- **Thiothixene** *(Navane).*
   c- **Zuclopenthixol** *(Clopixol).*
   d- **Flupenthixol** *(Fluanxol).*
2- *Similar* chemically & Pharmacology to the Phenothiazines.

4- Butyrophenones:

1- *Examples*: **Haloperidol** (Safenace, Haldol*)* & **Droperidol**
2- Similar to Chlorpromazine BUT STRONGER Anti-Dopamine effects.
3- STRONGER → Antipsychotic, Anti-Emetic & Extrapyramidal manifestations.
4- Uses:
   a- **Haloperidol** (Safenace, Haldol): Anti-psychotic in Schizophrenia.
   b- **Droperidol** + Fentanyl (Opioid Analgesic) → I.V. Neurolept Analgesia for minor operations. The emetic effect of Fentanyl is *Antagonized* by the Antiemetic effect of Droperidol.

5- Atypical Anti-Psychotic Drugs:

1- Examples :
   a- **Pimozide** *(Orap)* : Selective D_2-blocker specific on Limbic system.
   b- **Sulpiride** *(Dogmatil)* : Selective D_2-blocker specific on Limbic system.
   c- **Clozapine** (*Leponex*) : It blocks D_4 & 5-HT_2 receptors.
   d- **Risperidone** (*Risperdal*) : It blocks D_2 = 5-HT_2 receptors.
   e- **Olanzepine** (Zyprexa): It blocks 5-HT_2 > D_2 receptors.

2- Similar to other Anti-Psychotic drugs BUT:
   a- Less extrapyramidal side effects.
   b- Clozapine, Risperidone & Olanzepine are claimed to be *More* effective in Refractory cases of Schizophrenia & hey can improve the negative signs e.g. dementia, emotional blunting & poor socialization.

3- *Clozapine* has high incidence (1-2%) of Agranulocytosis.

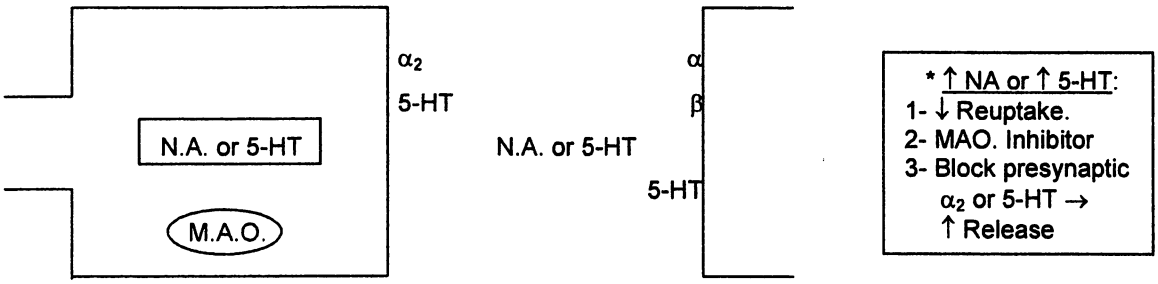
Phenothiazines	Benzodiazepine
1- Major tranquillizer → Anti-Psychotic	1- Minor tranquillizer → Anti-Anxiety
2- Block D_2 – Receptors	2- Stimulate Bz (ω) receptors
3- Extrapyramidal manifestations	3- No
4- A.N.S. manifestations	4- No
5- ↑ Epilepsy	5- Anti-Epileptic
6- No Dependence	6- Dependence & Addiction

Treatment of Affective (Mood) Disorders

- **Psychic Depression** is caused by functional deficit of the monoamines transmitters (Noradrenaline & Serotonin) in certain parts in the brain.
- **Mania** is caused by functional excess of monoamines.

Types of Depression	%	Features	Management
1- Reactive "Secondary" Depression.	60%	- Adverse life events, death, diseases & drugs.	- Spontaneous recovery. - Ministration.
2- Major "Endogenous" Depression.	25%	- Spontaneous. - Genetically determined. - Biochemical causes.	- Antidepressants. - Electro-Convulsive Therapy (ECT).
3- Bipolar Affective "Manic-Depressive" Disorder	15%	- Spontaneous. - Genetically determined. - Biochemical error.	- Lithium. ± Antidepressant. ± *Neuroleptic.*

Anti-Depressant Drugs
"Psycho-analeptics , Thymoleptics , Psychic Energizers



* *Classification Of Anti-Depressants:*

1- Monoamine Reuptake Inhibitors:
   a- *Tricyclic Antidepressants* → Cocaine-Like → ↓ Reuptake of *Both* NA & 5-HT
      Examples: Imipramine & Amitriptyline.
   b- *Selective Serotonin Reuptake Inhibitors (SSRI)* e.g. Fluoxetine.
   c- *Selective Noradrenaline Reuptake Inhibitors* e.g. Maprotiline.

2- Mono-Amine Oxidase Inhibitors (MAOI) e.g. Tranylcypromine.

3- Others e.g. Mianserine → Presynaptic α_2 & 5-HT Blocker → ↑ Release of Noradrenaline & Serotonin.

NB) Another Classification of Anti-Depressants:
1- Monocyclic: Tofenacin
2- Bicyclic:
a- Viloxazine: ↓ Uptake of Noradrenaline.
b- Zimelidine: ↓ Uptake of Serotonin.
3- Tricyclic:
a- Tertiary amines: Imipramine & Amitriptyline.
b- Secondary amines: Desipramine.
4- Tetracyclic:
a- Maprotiline: ↓ Uptake of Noadrenaline.
b Mianserine: Blocks presynaptic α_2 & 5-HT receptors.
5- Miscellaneous: Fluoxetine (SSRI).

I- Tricyclic Antidepressants (TCA)

* Members:

1- Imipramine *(Tofranil).*
2- Desipramine *(Norpramine).*
3- Clomipramine *(Anafranil).*
4- Amitriptyline *(Tryptizol).*
5- Nortriptyline *(Aventyl).*

* Pharmacokinetics of TCA:

1- Absorbed orally → Extensive hepatic first pass metabolism.
2- Highly bound to plasma & tissue proteins.
3- Highly lipid soluble. Pass easily BBB & Placental barriers.
4- Hepatic Metabolism:
   a- Change of Tertiary amines → Active Secondary amines :
      - Imipramine (? Active) → Active Desipramine.
      - Amitriptyline (Active) → Active Nortriptyline.
   b- Glucuronic acid conjugation → Inactive metabolites.
5- Excretion in urine mainly in conjugated form.

* Mechanism of Action of TCA:

1- They inhibit *Neuronal Uptake$_1$* of Noradrenaline & Serotonin → Cocaine-like → ↑ Inter-Synaptically.
2- Long use **(> 2-3 WEEKS)**:
   a- Down-Regulation of β-, presynaptic α_2-, & 5-HT_2 receptors.
   b- Up-Regulation of postsynaptic a_1-receptors (TCA have α_1-blocking effect).
   c- Expression of Gene & Synthesis of Brain-Derive Neuro-trophic factor.

* Actions of Tricyclic Antidepressants:

1- *Anti-Depressant Effect*:
   Effect appears after **2-3 WEEKS** ☹ —2-3 Weeks→ 😐 —2-3 Weeks→ ☹
   and lasts for **2-3 WEEKS** after stop of TCA.
2- SEDATION: Especially at beginning of treatment & in Normal individuals.
   Amitriptyline > Imipramine > Desipramine.
3- *Lower Seizure Threshold*.
4- *Anti-Cholinergic* (Anti-Muscarinic = Atropine-Like).
   Amitriptyline > Imipramine > Desipramine.
5- *Anti-Histaminic* (H_1-Block) & *H_2-Block*.
6- *Anti-Serotonin*.
7- *Alpha blocking* effect.

* **Therapeutic Uses of TCA:**

1- **P**sychic depression.
2- Some **P**anic & Phobic states.
3- **P**eptic Ulcer. TCA → Block both M- and H_2-receptors.Cocaine withdrawal.
4- Obsessive **c**ompulsive disorders (Clomipramine or BETTER Fluoxetine).
5- **C**ocaine withdrawal.
6- **C**hronic pain (± Phenothiazine major tranquilizer).
7- *Nocturnal enuresis* (Imipramine) & urinary incontinence in elderly.

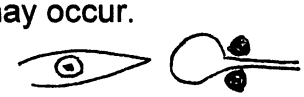
* Drug Interactions of TCA:

1- **Potentiate**:
   a- Sedatives e.g. Alcohol.
   b- Anti-cholinergics e.g. Major tranquillizers & Anti-Parkinsonians.
   c- Direct Catecholamines e.g. Adrenaline by # their Neuronal Uptake$_1$.
2- **Antagonize**:
   a- Indirect sympathomimetics e.g. Tyramine by # its Neuronal Uptake$_1$
   b- Antihypertensive effect of Guanethidine by # its Uptake$_1$.
   c- Antihypertensive effect of Clonidine & α-Methyl-Dopa due to Down- regulation of Presynaptic α_2-receptors.
3- **TCA + MAO-I** → Toxicity → Severe Atropine-like, Hypertension & Convulsions.

* *Side Effects & Toxicity Of TCA :*

1- Delayed onset of action (2-3 weeks).
2- **C.N.S.**: SEDATION, Seizures, Tremors, Confusion & Delirium.
3- **C.V.S.**:
   a- Postural hypotension (α_1-block).
   b- Tachycardia (Atropine-like).
   c- ***CARDIOTOXICITY*** → FATAL ARRHYTHMIAS.

4- **ATROPINE**-like effects → Blurring of vision, dry mouth, tachycardia, constipation & urinary retention. Paradoxical sweating may occur.
   Contraindicated in Glaucoma & Enlarged Prostate.



5- **Weight gain.**
6- **Allergic** Obstructive jaundice & Agranulocytosis.
7- **Acute Toxicity**: Common & FATAl.
   a- Manifestations: Excitement, Seizures, Arrhythmia & Atropine Like.
   b- Treatment: - ICU - Stomach wash + Charcoal.
   + Diazepam → Treats excitement & Seizures.
   + Phenytoin → Treats Seizures & Ventricular arrhythmias.
   + Physostigmine → treats Atropine-like effects.

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II- Selective Serotonin Reuptake Inhibitors (SSRI):

1- Fluoxetine *(Prozac)* :

1- Most prescribed antidepressant. *Dose*: 10-50 mg/day Orally.

2- Pharmacodynamics:
   a- SSRI → ↑ 5-HT → 2-3 Weeks → Down-regulation of 5-HT$_2$ receptors.
   b- Little effect on NA & Dopamine.
   c- Efficacy & time course are similar to TCA.
3- Therapeutic Uses:

   a- Mild to Moderate depression.
   b- Obsessive compulsive disorders.
   c- Eating disorders e.g. Bulimia nervosa.

4- Advantages of Fluoxetine over TCA:
   a- Less Adverse Effects → NO Anticholinergic (Allowed in Glaucoma patients) or CVS side effects or weight gain.
   b- Low acute toxicity → No Cardiotoxicity or Hepatotoxicity
   c- Little interactions & NO Interaction with food.

5- Adverse Effects of Fluoxetine:
   a- Anorexia, nausea & diarrhea.
   b- Anxiety, insomnia & mania.
   c- Increases aggression, violence & suicide.
   d- Fluoxetine + Melatonin or NAOI → Serotonin syndrome. May be FATAL.

NB) *Other SSRI* → Similar to Fluoxetine
2- Citalopram *(Cipram)* 3- Sertraline *(Lustral)*
4- Fluvoxamine *(Faverin)* 5- Trazodone *(Tritico)*

III- Selective Noradrenaline Uptake Inhibitors:

1- **Maprotiline** *(Ludiomil): It has NO major advantage over TCA.*

2- **Nomifensine** *(Merital): NO Sedation, CVS side effects or Anticholinergic → More suitable for the elderly depressed patients*

IV- Mono-Amine Oxidase Inhibitors (MAOI)

* *Types of MAO Enzymes*:

	M. A. O. - A	M. A. O. -B
1- Location :	1- Placenta, Gut mucosa, Liver & Brain.	1- Platelets, Liver & Brain.
2- Substrate :	2- NA & 5-HT.	2- Dopamine.
3- Selective Inhibitors :	3- Clorgyline & Moclobemide	3- Selegiline (Deprenyl).

Noradrenaline $\xrightarrow{\text{MAO-A}}$ Vanyl Mandelic Acid (VMA) → Urine (2-6.5 mg / day).
Serotonin $\xrightarrow{\text{MAO-A}}$ 5-Hydroxy-Indol Acetic Acid (5-HIAA) → Urine (1-10 mg / day).

* *Classification of MAO-I* :

A) Hydrazine Group:
1- Isocarboxazid *(Marplan).* 2- Phenelzine *(Nardil).* 3- Nialamide *(Niamde).*

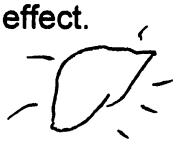
B) Non-Hydrazine Group:
1- **Tranylcypromine** (Parnate).
2- **Moclobemide** (Aurorix): A rapidly reversible MAO-A inhibitor.
3- Clorgyline: Selective MAO-A inhibitor.
4- Selegiline (Deprenyl): Selective MAO-B inhibitor → Anti-Parkinsonian.

* *Pharmacodynamics of MAO-I:*

1- Inhibition of MAO enzyme:
   a- Acute accumulation of Intra-cytoplasmic Noradrenaline & serotonin.
   b- After long use (2-3 WEEKS) → Down-regulation of β- & 5-HT receptors.
   c- MAOI ↑ monoamines in CNS & body BUT ↓ VMA & HIAA in urine.
2- Anti-Depressant effect of MAOI appear ☹ 2-3 Weeks ☺ 2-3 Weeks ☹ after 2-3 WEEKS & Lasts for 2-3 WEEKS after stop of MAO.I.

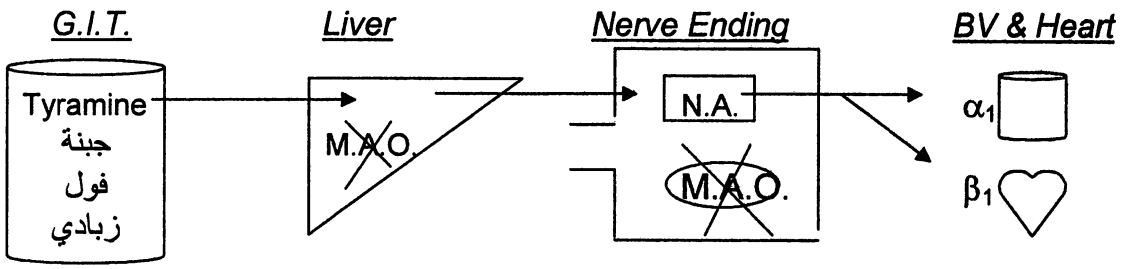
* Side Effects & Toxicity of MAO-I:

1- Delayed onset (2-3 weeks)
2- C. N. S.: Excitation → Insomnia, hyperhidrosis, hallucination & Seizures.
2- C. V. S.: Hypotension & Postural hypotension.
3- Some has **Atropine-like** effect.
4- Weight gain.
5- HEPATOTOXIC.



* *Drug Interactions of MAO-I:*

1- Cheese Reaction *(NOT with Moclobemide or Selegiline):* Eating or drinking foods that contain TYRAMINE or DOPA such as Aged cheese, Broad beans or Yogurt → Severe Hypertension (Pheochromocytoma-like reaction).
Treatment by IV Phentolamine or Nitroprusside ± β-Blocker.



2- I-DOPA (Anti-Parkinsonian) → Agitation & Hypertension.
3- Potentiates Indirectly Acting Sympathomimetics e.g. Amphetamine.
4- Reverse Hypotensive effect of Reserpine & Guanethidine.
5- SSRI (Fluoxetine), Melatonin & Meperidine → Serotonin Syndrome → Excitation, Hyperthermia, Cardiac arrhythmia, Hypotension, Tremors & Coma. May be FATAL.
6- MAOI + TCA → Toxicity.
7- MAO-I → Enzyme inhibitors → Potentiate other drugs e.g. Alcohol.

V- Other Anti-Depressants

- Mianserine *(Tolvon):*
a- Blocks presynaptic α_2- & 5-HT_2 receptors → Increase release of NA & 5-HT.
b- NO CVS side effects or Atropine-like → Preferred in Elderly depressed patients.
c- Causes Sedation.

Lithium Carbonate (Prianil)

1- Antimanic & Mood Stabilizing agent.
2- Used mainly as mood stabilizing in Bipolar affective disorder.
3- Not very effective in acute mania → Weak & Slow onset.

* Pharmacokinetics:

1- Well absorbed orally.
2- Distributed in total body fluid. Vd = 0.5-0.6 l/kg.
NOT bound to plasma proteins.
3- NO Hepatic Metabolism.
4- Excreted in urine & other body fluids (Tears, Saliva, Sweat & Milk).
a- Urinary excretion of lithium is INCREASED by:
- Na^+ load e.g. NaCl.
- Alkalinizers of urine e.g. $NaHCO_3$.
- Osmotic diuretics e.g. Mannitol.
- Acetazolamide & Triamterene.

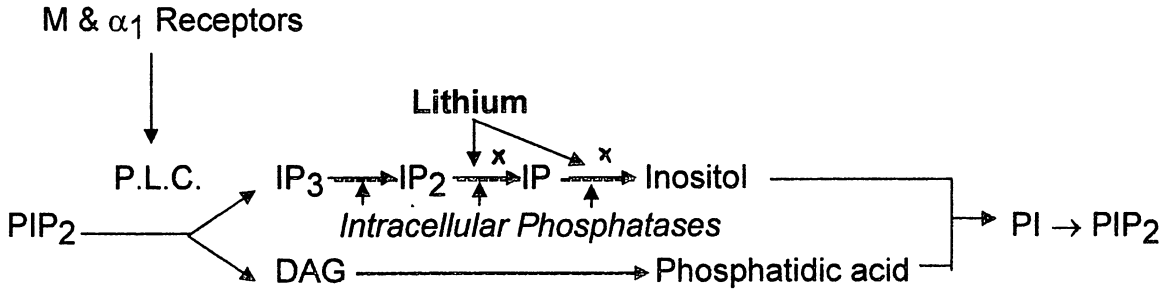
b- Urinary excretion of lithium is DECREASED by:
- Hyponatremia (Low salt intake, vomiting & diarrhea).
- Most of Diuretics e.g. Thiazides, Frusemide & Spironolactone.
- Most of NSAID.

* Mechanism of Action of Lithium:

1- Electrolytes and Ion transport: It has similar properties to Na^+. It can substitute Na^+ in generating action potential, but it is retained inside the cells.

2- Effect on Second Messengers:

a- Lithium inhibits the conversion of inositol diphosphate (IP_2) to inositol monophosphate (IP) and inositol, an essential step in the normal recycling of membrane phosphoinositids, leading to depletion of phosphatidylinositol-4,5-biphosphate (PIP_2), the membrane precursor of IP_3 and DAG. This will cause selective depression of the overactive neurons that contribute to the manic state.



b- Lithium also inhibits the activation of adenylate cyclase enzyme induced by hormones (ADH & Thyrotropine) and neurotransmitters (NE).

* Therapeutic Uses of Lithium:

Dose: 1200-1800 mg/day. *Therapeutic Blood level* = 1 meq./liter.

1- Bipolar affective (Manic-Depressive) disorder.
(NB: Other drugs e.g. Carbamazepine & Lamotrigine).
2- Prophylaxis of recurrent endogenous depression.
3- Schizo-affective disorders.
4- Management of aggressive & violent behavior in prisoners.
5- Prophylaxis of tardive dyskinesia induced by antipsychotic drugs. Lithium prevents the development of dopamine supersensitivity.
6- Syndrome of Inappropriate ADH Secretion.

* Adverse Effects & Toxicity of Lithium:

1- C. N. S.: Tremors, dyskinesia & Confusion.

2- Thyroid: Smooth benign enlargement.

3- C. V. S.: Depresses sinus node.

4- Renal:
a- Initial polydipsia and polyuria. May be through antagonizing the effect of ADH on adenylate cyclase enzyme of the distal convoluted tubules i.e. nephrogenic diabetes insipidus.
b- Nephrotoxic. Frequent urine analysis is required.

5- Edema: Na^+ and water retention, may be via increased release of aldosterone

6- Weight gain, partially by edema formation.

7- During Pregnancy & Lactation:
a- Dysmorphogenesis (Teratogenecity).
d- Lithium is secreted in milk and affects suckling baby leading to lethargy.

8- Skin: Acniform eruptions and folliculitis.

9- Leukocytosis, an effect on leukpoeisis.
This effect could be therapeutic in patients with leukopenia.

10- Diminished sexual functions.

11- Acute toxicity (Overdose):
a- Manifestations:
- At plasma levels 2-2.5 meq/L: Confusion (important sign), drowsiness, dizziness, ataxia, severe tremors & vomiting.
- At plasma levels > 2.5 meq/L: Clonic movements of limbs, convulsions, cardiac arrhythmias and circulatory collapse then coma and even death.

b- Treatment :
- Stop lithium.
- NaCl and $NaHCO_3$ infusion.
- Osmotic diuretics.
- Aminophylline.
- The most important item is *hemodialysis*.

Analgesics (مسكنات الألم)

These are drugs that relieve the pain centrally without loss of consciousness or other sensations.

*Classification of Analgesics:

A) Central Analgesics = Proper Analgesics:

1- Narcotic Analgesics e.g. Morphine.
2- Anti-pyretic Analgesics e.g. Aspirin.

B) Peripheral Analgesics = Not Proper Analgesics:

1- Causal:
a- Ergotamine & Caffeine in Migraine headache.
b- Nitroglycerine in Anginal pain.
c- Antacids in Peptic ulcer.
d- Anti-spasmodics e.g. Atropine in colic.
e- Colchicine in Gouty arthritis.

2- Non-Causal;
a- Physical protective e.g. Demulcents on irritated surface.
b- Astringents by precipitating surface proteins of nerve receptors.
c- Counter-irritants.
d- Local anesthetics.
e- Obtundents by destruction of exposed nerve terminals in tooth cavity.

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Central Analgesics

	Narcotic Analgesics	Anti-pyretic Analgesics
1- Example	Morphine	Aspirin
2- Potency	Potent, effective in *ALL* types of pain *Especially* deep visceral *But Not* itching	Less potent, effective in superficial pain
3- Mechanism of Action	Central → Spinal & Supra-spinal	- Central on thalamus - Peripheral as anti-inflammatory
4- With analgesia	Stupor & Drowsiness	Lowers elevated body temperature to normal
5- Long use	Tolerance *Then* Dependence	No Tolerance & No Dependence

Narcotic Analgesics

These are drugs that relieve the pain centrally, *But* in large dose they cause stupor & drowsiness, & on long use they produce tolerance & dependence.

*Classification Of Narcotic Analgesics:

1-Phenantherene Opium Alkaloids: Morphine & Codeine.

2-Semisynthetic Morphine Derivatives *(Phenantherenes)*:
- a- Di-acetyl-morphine (Heroin).
- b- Di-hydro-morphinone
- c- Oxymorphone
- d- Di-hydro-codeinone
- d- Oxycodone

3-Synthetic Morphine Substitutes *(Non-Phenantherenes)*:
- a- Meperidine
- b- Fentanyl
- c- Methadone
- d- Dextropopoxyphene

4-Mixed Agonist-Antagonist Narcotic Analgesics:
- a- Pentazocine
- b- Buprenorphine
- c- Nalbuphine
- d- Butorphanol

Opium Alkaloids

Opium is the air-dried milky juice of incised unripe fruit capsules of *Papaver somniferum* (Poppy seeds).

*Classification of Opium Alkaloids:

A)Phenantherene Opium Alkaloids:

1- Morphine → 10% of Opium
2- Codeine → 1% of Opium
} Narcotic, Analgesic & Addiction.

3- *Thebaine → Convulsive.*

B)Benzyl-Isoquinoline Opium Alkaloids;

1- Papaverine → Spasmolytic
2- Narcotine → Anti-tussive
} *Not* Narcotic, *Not* Analgesic & *NO* Addiction

3- *Narceine → Convulsive.*

Morphine

Natural Phenantherene Opium Alkaloid (10% of Opium)

* Kinetics:

1- Absorption:
- a- Orally, *But* → Low (25 – 30 %) Oral Bioavailability.
- b- Better absorbed after S.C. & I.M. injections.
- c- In shock → Slow Diluted I.V. injection.

2- Distribution: All over the body & passes B.B.B. & Placental Barrier →
- a- During pregnancy → Addiction of Fetus.
- b- During labor → Neonatal asphyxia → Treat by *Naloxone* (I.M. to mother before labor or Intra-umblical to baby after labor).

3- Metabolism:
- a- Extensive (70-75%) Hepatic First Pass Metabolism.
- b- Conjugated with Glucuronic acid by Hepatic Microsomal Enzymes:
  - **Morphine-6-Glucuronide** → More Active than Morphine.
  - Morphine-3-Glucuronide → Inactive.
  - Deficient in extremities of age → Supersensitivity.

4- Excretion:
- a- Saliva → Test for racing horses.
- b- Stomach → Stomach wash in all cases of poisoning.
- c- Bile → Entero-Hepatic circulation.
- d- Milk → Affect suckling baby.
- e- Urine → *Major* route of excretion.

5- $t_{\frac{1}{2}}$ (2 – 3 hours) & Duration of action (6 – 8 hours).

* Mechanism Of Action Of Morphine:

Morphine stimulates specific *Opioid* = *Opiate* receptors in CNS & Periphery.

A) Types of Opiate (Opioid) Receptors:

1- **Mu (μ_1 & μ_2)**: Analgesia (Spinal & Supra-spinal), Euphoria, Sedation, Dependence, ↓ R.C., Miosis & Constipation.
2- **Kappa (κ_1, κ_2 & κ_3)**: Analgesia (Spinal & Supra-spinal), Dysphoria, Psychotomimetic, Less ↓ R.C. & Less Miosis
3- **Delta (δ_1 & δ_2)**: Analgesia (Spinal & Supra-spinal) & Constipation.
4- **Sigma (σ)**: Dysphoria & Hallucination.

B) Mechanism Of Opiate (Opioid) Receptors:

They are membrane receptors coupled to G-protein:
1- ↓ Adenylate cyclase → ↓ cAMP.
2- Open K^+-Channel → Hyperpolarization.
3- Block Ca^{2+}-Channel → ↓ Release of transmitters & mediators.

C) Endogenous Opio-peptides:

1- Endorphins (β-).
2- Enkephalins (Met- & Leu-)
3- Dynorphins (A- & B-).
4- Endomorphins

Enkephalins	Endorphins
Met- & Leu-	β-
Neuro-transmittre	Neuro-hormone
δ-Agonist	μ-Agonist
Penta-peptide (5 Amino-acids)	Polypeptide (31 amino-acids)
Rapid metabolism by Peptidase	Slow metabolism
Short duration	Long duration

* Actions Of Morphine:

All actions of morphine are mediated via stimulation of Opiate (Opioid) receptors in C.N.S. & periphery.

1- C. N. S.:

Mixed Stimulation & Depression of certain parts of C.N.S.

Depressant Actions	Stimulant Actions
1-Analgesia	1-Euphoria
2-Narcosis	2-Excitation in some females & Animals
3- ↓ R.C. → Hypoventillation & Hypoxia	3- ↑ 3rd Cranial nerve → Miosis (PPP)
4- ↓ Cough center → Anti-tussive	
5- ↓ V.M.C. → Hypotension	4- ↑ Vagal center (CIC) → Bradycardia
6- ↓ Vomiting center (Large dose)	5- ↑ C.T.Z. (Small dose)→ Nausea & vomiting
7- ↓ H.R.C. → Hypothermia	
8- ↓ Hormones: ACTH, FSH & LH.	6- ↑ A.D.H.
9- ↓ Polysynaptic spinal reflexes e.g. withdrawal reflex	7- ↑ Monosynaptic spinal reflexes e.g. Stretch reflex (Knee jerk)
	8- Lowers seizure threshold → ↑ Epilepsy
	9-Trunkal rigidity due to ↑ Hippocampal pyramidal cells

A) Depressant Actions:

1- Analgesia:

a- Effective in *All* types of pain *especially* Deep visceral pain.
b- Not effective in itching. Morphine is a Histamine-releaser.
c- Morphine affects pain perception & integration:
- ↓ Release of Substance-P & Glutamate in Substantia gelatenosa (part of Dorsal horn in spinal cord) by spinal & supra-spinal mechanisms.
- Sensory cortex → ↓ Pain perception.
- Frontal cortex → Alters psychological reaction to pain → Indifference.
- Narcosis & hypnosis are adding factors.

2- Narcosis: Stupor & drowsiness → Lethargy → Deep dreamless sleep.

3- ↓ R.C.: ↓ Its sensitivity to CO_2 → Hypoventillation & Hypoxia.

4- ↓ Cough center → Anti-tussive.

5- ↓ V.M.C. → ↓ Sympathetic → V.D. & Hypotension.

6- ↓ Vomiting center (In Large dose).

7- ↓ Heat regulating center → Hypothermia.

8- ↓ Release of hormones e.g. ACTH & Gonadotrophins (FSH & LH).

9- ↓ Polysynaptic spinal reflexes e.g. Withdrawal reflex.

B) Stimulatory Actions:

1- Euphoria mostly due to relief of pain. In absence of pain → Dysphoria.

2- Excitation in some human females & some animal species e.g. Horse & mouse.

3- ↑ Third cranial nerve nucleus (Edinger Westphal ganglia) → Miosis → P.P.P.

4- ↑ Vagal center (C.I.C.) → Bradycardia.

5- ↑ C.T.Z. (In Small dose) → Nausea & vomiting.

6- ↑ A.D.H. release.

7- ↑ Monosynaptic spinal reflexes e.g. Stretch reflex (Knee jerk) & Straub's reaction in mice & rat.

8- Lowers seizure threshold → Worsens Epilepsy.

9- Trunkal rigidity due to ↑ of Hippocampal pyramidal cells.

2- *A. N. S.*: ↓ Sympathetic (↓ VMC) & ↑ Parasympathetic (↑ CIC)

3- *Eye* → **Miosis → Pin Point Pupil (PPP)**

1- **Morphine** → C.N.S. → ↑ Opiate Receptors of III C.N. Nucleus (Edinger Westphal ganglia) → Oculomotor Nerve → Ciliary Ganglia (N_N) → Eye → A.Ch. → ↑ M.R. of C.P.M. → Severe Miosis (Pin Point Pupil)

2- **P.P.P. of Morphine can antagonized by**:
   a- Systemic Naloxone → Block Opiate receptors in C.N.S.
   b- Systemic Ganglion Blockers → Block Ciliary Ganglia
   c- Topical Atropine → Block M-receptors on C.P.M.

3- Morphine in some human females → Mydriasis (due to excitement).

4- *C. V. S.* → **Bradycardia & Hypotension**

1- Small therapeutic dose → No effect.
2- Large dose especially I.V. → Hypotension:
   a- ↓ VMC & ↑ Vagal center (CIC)
   b- Direct veino-dilator effect.
   c- Release of *Histamine* → V.D.

5- *Respiratory System:*

1- ↓ R.C. → ↓ Sensitivity to CO_2 → ↓ Rate & Tidal volume → Hypoventilation & Hypoxia.
2- ↓ Cough center → Central Anti-tussive.
3- Histamine release → Bronchospasm especially in susceptible asthmatic patients.

6- *Smooth muscle* → **Spasmogenic** effect.

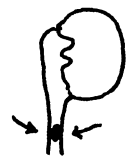
7- *G. I. T.* → **Spasmogenic → Constipation**

1- ↓ All secretions (except salivary).
2- **Spasmogenic** → ↓ Propulsive peristalsis, ↑ Segmental contraction & Spasm of sphincters (especially anal) → ↓ Transit of intestinal contents → Water absorption → Hard fecal matter.
3- ↓ Defecation reflex.
4- Patient is unaware of constipation.
5- *The spasmogenic effect of Morphine on GIT*:
   a- Due ↑ μ & δ opio-receptors.
   b- Antagonized completely by Naloxone & Partially by Atropine.
6- Loperamide & Diphenoxylate → Morphine-like on GIT → Constipation → Treat diarrhea with minimal or No CNS actions.

8- Biliary Tract → **Spasmogenic**

Spasm of Biliary duct & Sphincter of Oddi → ↑ Intra-biliary:
1- Avoid after cholecystectomy.
2- In biliary colic → Add Atropine to Morphine.

9- *Urinary Tract* → **Spasmogenic**



1- Spasm of Ureter → In renal colic → Add Atropine to Morphine.
2- retention of Urine → Spasm of sphincters & ↓ Micturition reflex.
3- Oliguria → ↑ A.D.H.

10- *Uterus:*

No effect *but* Morphine passes placental barrier → Neonatal asphyxia.

11- *Skin:* Histamine release → Itching & Triple response.

12- *Metabolism* → ↓ B.M.R.

13- *Immuno-suppressive.*

NB) Tolerance to Morphine:

1- Occurs after continued use of Morphine for 10-14 days.
2- Due to ↓ Endogenous Endorphins & Enkephalins or ↑ Adenylate cyclase activity.
3- Affects *Mainly* Analgesia & ↓ R.C. & *Not* PPP, constipation or excitation.
4- Followed by dependence Both Psychic & Physical → Addiction.
5- Cross Tolerance & Dependence between the Narcotic Analgesics.

* Therapeutic Uses Of Morphine:

Dose: S.C. & I.M. (10 mg), I.V. (5 mg) & Oral (30 mg).

1- Pain: Analgesic in *Severe Visceral Pain*

a- Cardiac pain e.g. Myocardial infarction
b- Cancer pain especially in terminal stages
c-Colic: Add Atropine in Biliary & Renal colic.
d- Fracture bones (Except Skull, Morphine is contraindicated in Head injury).
e- Post-operative Except Biliary & Eye operations.

2- Pre-anesthetic medication: *(See Anesthesia)*

a- Morphine *WAS* used to provide Analgesia, amnesia & sedation. *Add* Atropine.
b- *Disadvantages*: - Delays awakening from anesthesia - ↓ R.C.
- Miosis → Interfere with stages of anesthesia - Vomiting
- Bronchospasm - Postoperative constipation & retention of urine

3- Pulmonary Edema due to Acute Left Ventricular Failure:

a- Veino-dilator → ↓ VR → ↓ E.D.V. → ↓ Preload & ↓ Pulmonary congestion.
b- Sedation → ↓ Sympathetic → Arterial V.D. → ↓ T.P.R. → ↓ After-load.
c- Slow respiration.

4- Primary Neurogenic shock.

5- Anesthesia → I.V., Intra-thecal & Epidural.

* Contraindications of Morphine:

1- Head injury:
   a- Miosis → Interfere with proper diagnosis.
   b- Morphine ↓ R.C. → ↑ CO_2 → Cerebral V.D. → ↑ Synthesis of C.S.F. → ↑ Intra-cranial tension → More ↓ R.C.
2- ↑ Intra-cranial tension.
3- Epilepsy.
4- Respiratory diseases e.g. Asthma & C.O.P.D.
5- Acute abdomen → Morphine → Analgesia → Interfere with proper diagnosis.
6- Pregnancy & Labor:
   a- Pregnancy → Addict fetus → Withdrawal symptoms after labor.
   b- Labor → Neonatal asphyxia.
7- Liver disease → Deficient metabolism.
8- Extremities of age → Deficient metabolism.
9- Myxedema → ↓ Metabolism → More ↓ CNS, ↓ B.M.R. → Myxedema coma.
10- Alone in biliary & renal colic.
11- Allergy to morphine.
12- History of Addiction to Morphine or other opiates.

* Adverse Effects Of Morphine:

1- Interfere with proper diagnosis of Head injury & Acute abdomen.
2- ↓ Respiration
3- P.P.P.
4- Nausea & Vomiting
5- Bronchospasm
6- Constipation
7- Retention of urine
8- Neonatal asphyxia
9- Itching
10- Tolerance & cross-tolerance with other Opioids.

11- *Acute Morphine Poisoning*:

a- *Manifestations*: Coma + PPP + Hypoventillation, Hypoxia, Hypotension & Hypothermia.

b- *Cause Of Death* → Respiratory Failure.

c- *Treatment*:
- Artificial respiration. No pure O_2 → Apnea.
- Stomach wash in *Every* case even after parenteral poisoning. Use K-Permanganate + Charcoal + $MgSo_4$.
- Specific Morphine Antagonists e.g. **Naloxone** (0.4 mg I.V.).

12- *Chronic Poisoning* → **Addiction**:

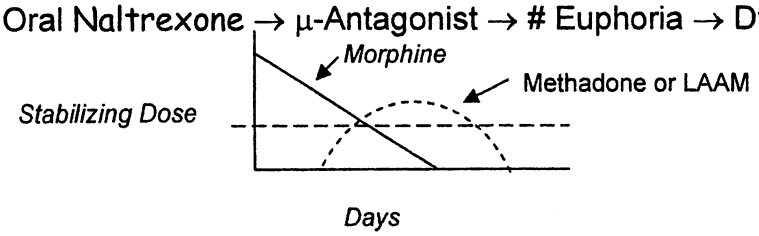
a- Tolerance → Psychic Dependence → Physical Dependence.

b- *Due to* ↓ Endogenous Endorphins & Enkephalins.

c- *The addict* → PPP, constipation, Psychosis (drug seeking habit) & moral deterioration.

d- *Sudden stop* of Morphine or *use of Morphine antagonist* → **Withdrawal or Abstinence syndrome** → Psychic craving for Morphine, Anxiety, yawning, lacrimation, rhinorrhea then reversal to all actions of morphine → Excitation, severe pain, fever, mydriasis, hyperventilation, hypertension, tachycardia, diarrhea & urination. All these symptoms disappear on taking morphine.

e- *Management*:
- *Hospitalization* + Psychotherapy.
- *Gradual withdrawal* of Morphine till the stabilizing dose.
- *Gradual substitution* with either Methadone or Levo-Methadyl acetate (LAAM, Levo-α-acetyl methadol) → Similar to Morphine *But Less* withdrawal manifestations.
- *Gradual withdrawal* of Methadone or LAAM.
- Clonidine → Control of many withdrawal symptoms.
- Acupuncture → ↑ Release of endogenous endorphins & enkephalins.
- Oral Naltrexone → μ-Antagonist → # Euphoria → Dysphoria.



II- Codeine (Methyl-Morphine)

1- Phenantherene Opium Alkaloid, 1% of Opium.
2- In the body, 10% Codeine → Morphine.
3- Kinetics → Similar to Morphine *But*:
   a- Better oral bioavailability → 50%.
   b- Shorter duration → 2 – 4 hours.
4- Dynamics → Similar to Morphine *But*:
   a- Weaker (1/5 Morphine) as Analgesic, Constipation & Addiction.
   b- As potent as morphine as an **Anti-tussive**.
   c- Large dose → ↓ R.C., ↓ V.M.C. & Excitation → Epilepsy in Children.
5- Therapeutic Uses:
   a- **Anti-Tussive** (15-30 mg at bed time) in Dry useless cough & Dangerous cough e.g. Post-operative.
   b- **Analgesic** (10 mg) in Mild & Moderate visceral pain ± Aspirin & Paracetamol.

	Morphine	Codeine
1- Chemistry	Morphine	Methyl-morphine
2- % of Opium	10%	1%
3- Oral Bioavailability	25 – 30 %	50%
4- Duration of action	6 – 8 hours	2 – 4 Hours
5- Anti-tussive	Potent	Potent
6- Analgesia	Potent	Weaker (1/5)
7- Constipation	Potent	Weaker
8- Addiction	Highly	Weaker
9- Large dose	↓ RC, ↓ VMC & Coma	↓ RC, ↓VMC & Excitation
10- Use	Severe Visceral pain	Mild Visceral pain & Antitussive

* *Benzyl-Isoquinoline Opium Alkaloids*

1- Papaverine → **Spasmolytic**:

a- *Smooth muscle* e.g. Bronchial, Biliary, GIT, Urinary & Uterus → Useful in Colic.
b- *B.V.* → V.D. → Useful in Coronary, Pulmonary & Peripheral thrombosis.

2- Narcotine (Noscapine) → Non-Narcotic Central **Anti-tussive**.

Semi-Synthetic Morphine Derivatives (Phenantherenes)

1- Di-Acetyl-Morphine (Heroin):
   a- Highly Lipid Soluble → Concentrated in Brain → De-acetylated → Morphine.
   b- Snuff or I.V. b- Short t ½ → ½ Hour c- Highly Addictive.
2- Dihydro-Morphinone & Methyl-Dihydro-Morphinone → Stronger than Morphine
3- Dihydro-Codeinone → Stronger than Codeine → Useful as an Anti-tussive.
4- Ethyl-Morphine → Counter-Irritant → Eye drops in corneal ulcer & iritis.
5- Apomorphine → Direct Dopamine-Agonist:
   a- ↑ C.T.Z. → Central emetic b- Anti-Parkinsonian c- Aphrodesiac.

Synthetic Morphine Substitutes (Non-Phenantherenes)

1- Meperidine (Pethidine)

A) *Chemistry* → Synthetic Phenylpiperidine.

B) *Kinetics*:

1- 50% Oral Bioavailability.
2- Quick onset & Short duration (2 – 4 hours).
3- Metabolized in liver →
   a- Meperidenic acid → Inactive → Conjugated with glucuronic acid → Urine.
   b- Nor-Meperidine → Active → Excitation & Convulsions.

C) *Dynamics* → Morphine-Like + Atropine-Like

1- Less Analgesia (1/10 Morphine)
2- Less ↓ R.C.
3- Less Emetic
4- Less Addiction
5- **Atropine-Like**
6- No P.P.P. may cause Mydriasis
7- No Constipation
8- No Narcosis (No Hypnosis)
9- No Anti-tussive
10- Local irritant *then* Local anesthetic.
12- Large dose → Excitation (Atropine-like + Nor-meperidine).
13- ↑ A.D.H.
14- Antagonized by Naloxone
15- *Drug Interaction*: Meperidine + MAO.I → Severe ↓ RC, excitation & convulsions

D) *Therapeutic Uses*: 50 – 100 mg Orally or I.M.

1- Severe Visceral pain e.g. Myocardial infarction.
2- Alone in Biliary & Renal colic.
3- Pre-anesthetic medication (Better than Morphine).
4- Obstetric Analgesia: Meperidine + Hyoscine → Twilight Sleep → Less ↓ Fetal R.C.

	Morphine	Meperidine
1- Nature	Natural Phenantherene Opium	Synthetic Phenyl-piperidine
2- Oral efficacy	25 – 30 %	Better 50 %
3- Metabolism	Active Morphine-6-Glucuronide Inactive Morphine-3-Glucuronide	Inactive Meperidinic acid Active Nor-meperidine
4- Onset	Slower	Quicker
5- Duration	Longer (6 – 8 hours)	Shorter (2 – 4 hours)
6- Analgesia	Stronger	Less (1 / 10)
7- ↓ R.C.	Stronger	Less
8- ↑ C.T.Z.	Stronger	Less
9- Addiction	Stronger	Less
10- Atropine-like	NO	Atropine-like
11- Pupil	P.P.P.	No
12- G.I.T.	Constipation	No
13- Narcosis	Narcotic	No
14- Anti-tussive	Anti-Tussive	No
15- Local actions	NO	Local irritant → Local anesthetic
16- Large dose	Coma	Excitation
17- A.D.H.	↑ A.D.H.	↑ A.D.H.
18- Antidote	Naloxone	Naloxone
19- Uses	Not in labor , Not alone in colic	Obstetric analgesia & Alone in colic

2- Fentanyl *(Sublimaze)*

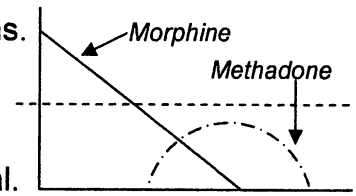
1- Derivative of *Meperidine*.
2- **Strong** μ-Agonist → **Strong** Analgesic → **80** Times > Morphine
3- *High Lipid solubility*: I.V. → Rapid Onset + Short duration (Redistibution)
4- Used as *I.V. Anesthesia*:
   a- Fentanyl alone, *But* → Vomiting.
   b- Fentanyl + Droperidol (Major tranquillizer) → *Neurolept- Analgesia*
   c- Fentanyl + Droperidol + Nitrous oxide → *Neurolept-Anesthesia*
   NB) The emetic effect of Fentanyl is # Anti-emetic effect of Droperidol.
5- *Adverse Effects* → Vomiting, Marked ↓ R.C. & ↑ Muscle tone → Trunkal rigidity.

N.B.) Meperidine Derivatives:

1- Alfentanyl *(Alfenta)* → *1/3 – 1/4 < Fentanyl* } *I.V. Anesthesia*
2- Sufentanyl *(Sufenta)* → *10 times > Fentanyl* }
3- Loperamide *(Imodium)*:
   a- Morphine-like on **G.I.T.** → Constipation → Treat Diarrhea.
   b- Not pass B.B.B. → **No** C.N.S. actions.
4- Diphenoxylate *(+ Atropine → Lomotil)*:
   a- Morphine-like on **G.I.T.** → Constipation → Treat Diarrhea.
   b- Some Lipid solubility → Some B.B.B. → **Some C.N.S.** → Some Narcosis.
   c- Large Dose of Lomotil especially in Children → Flush (Atropine) + Narcosis (Diphenoxylate)

3- Methadone *(Amidone)*:

1- *As* potent as Morphine.
2- *Better* Oral Bioavailability.
3- *Longer* t ½ = 1 – 2 days → Less withdrawal manifestations.
4- *Local* anesthetic effect.
5- *Uses*:
   a- Analgesic in Severe visceral pain e.g. Terminal cancer.
   b- To substitute Morphine & Heroin during their withdrawal.



NB) Levo-Methadyl Acetate (L-α-Acetyl-Methadol "LAAM) is an alternative.

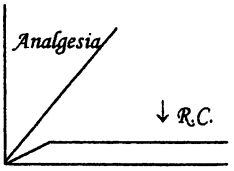
4- Dextro-Propoxyphene *(Doloxene)*:

1- Derivative of Methadone.
2- Analgesic = Codeine = 1/5 Morphine → Useful as Analgesic ± Aspirin & Parcetamol.
3- Weak Anti-Tussive.
4- Mild dependence.
5- Large dose → ↓ R.C. & Excitation.

5- Tramadol *(Tramal)*:

1- Similar to Dextro-Prpoxyphene.
2- Analgesic effect → ↑ Opiate receptors & ↓ Uptake of Noradrenaline & Serotonin.

Mixed Agonist (κ) - Antagonist (μ) Narcotic Analgesics



1- IF NO Morphine addiction → Kappa (κ)-Agonist → Analgesic.
2- IF Morphine Addiction → μ-Antagonist → Withdrawal manifestations.
3- Weak ↓ R.C. (Partial agonist) → Low ceiling effect.
↑ Dose of these drugs → More Analgesia But No More ↓ R.C.
4- Mild dependence → Mild withdrawal manifestations.

	μ	κ	σ	Remarks
1- Pentazocine	Antagonist	Agonist	Agonist	30-60 mg IM,SC, PO. Dysphoria, ↑ Heart & ↑ Bl.p.
2- Dezocine	Antagonist	Agonist		
3- Butorphanol	Antagonist	Agonist	-	2 mg IM. ↑ Heart & ↑ Bl.p.
4- Nalbuphine	Antagonist	Agonist	Agonist	10 mg IM Dysphoria
5- Meptazinol	Antagonist	Agonist		
6- Buprenorphine	P.A.	Antagonist	-	0.4 - 0.8 IM & SL

Narcotic Antagonists

- Opiate receptor antagonist.
- Block all actions (Therapeutic & Toxic) of Morphine & other Opioids.
- No effect on other C.N.S. Depressants e.g. Benzodiazepines.

1- Naloxone (Narcan):

1- Pure antagonist. More selective on μ-receptors.
2- Short t ½ = 1 hour → Has to be repeated.
3- Therapeutic uses:
a- Acute Morphine poisoning → 0.4 mg I.V. may be repeated.
b- Opioid-induced Neonatal asphyxia → Mother (IM) or Neonate (Intra-umblical).
c- Diagnosis of Opioid addiction → S.C. → Withdrawal manifestations e.g. Mydriasis.

2- Nalmefene → Similar to Naloxone But Longer t ½

3- Naltrexone:

1- Similar to Naloxone → Pure antagonist, more selective on μ-receptors.
But → Stronger, Longer & Effective orally.
2- Uses: 50 mg
a- Orally to maintain the Opiate-free state of treated addict.
b- Acute Morphine poisoning.

4- Nalorphine:

1- Mixed Agonist (κ & σ) and Antagonist (μ) narcotic antagonist.
2-Actions & Uses:
a- IF NO Morphine Addiction→ κ & δ - Partial Agonist → Narcotic analgesic But Dysphoria and hallucinations.
b- IF Acute Morphine Poisoning → μ-Antagonist → Treatment Opiate-induced Acute poisoning and Neonatal asphyxia.
c- IF Morphine Addiction → μ-Antagonist → Withdrawal manifestations e.g. Mydriasis → Useful in diagnosis of opiate addiction.

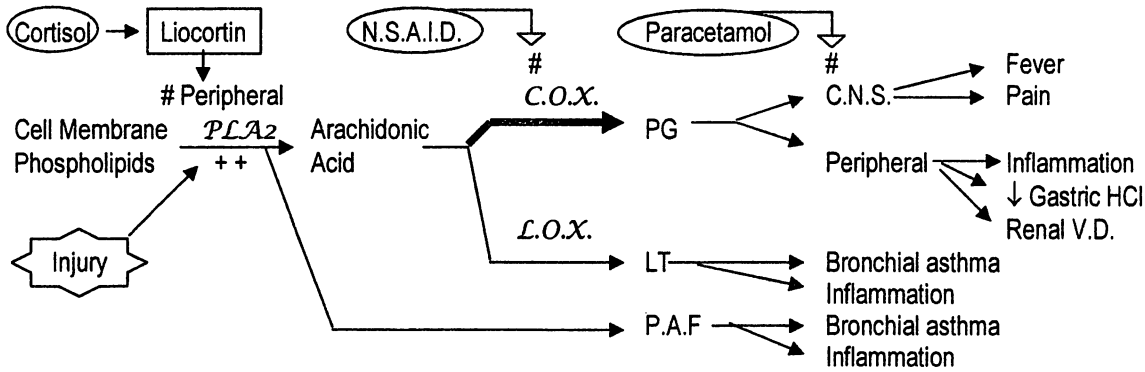
5- Levalorphan → Similar to Nalorphine.

NB) Drugs & Opiate Receptors:

1- **Agonists**: Morphine, Meperidine & Fentanyl.
2- **Antagonists**: Naloxone & Naltrexone.
3- **Mixed Agonist-Antagonist**: Pentazocine & Levalorphan

Non-Narcotic Analgesics = Antipyretic Analgesics = Non-Steroidal Anti-Inflammatory Drugs (NSAID)

- CNS depressants that relieve the pain centrally without narcosis.
- They lower elevated body temperature to normal.
- Most of them (except Paracetamol) have anti-inflammatory and anti-rheumatic effects = Non-Steroidal Anti-Inflammatory Drugs (NSAID).



* Mechanism of Action of NSAID:

They ↓ COX → ↓ Synthesis of prostaglandins (PGs), Prostacyclin (PGI2) & Thromboxane-A_2 (TXA_2).

* Types of Cyclo-Oxygenase Enzymes (C.O.X.):

A) **COX-1**: Constitutive → Physiological
1- Stomach ↓ HCl (Prevent peptic ulcer).
2- Kidney → Renal VD.

B) **COX-2**: Inducible by inflammation → Pathological
Infection → Toxins → IL-1 & TNF → ↑ COX-II → ↑ PG → Inflammation
1- C.N.S.:
a- Hypothalamus → HRC → Fever. b- Thalamus → Pain
2- Periphery → Inflammation:
a- Sensitize Nociceptors to Histamine, bradykinin & 5-HT → Pain.
b- Potentiate effect of histamine & bradykinin →
- V.D. → Redness & hotness.
- ↑ Capillary permeability → Edema.
c- Enhance other cytokines

- **NB) Drugs & COX Enzymes:**

1- Most of NSAID e.g. Aspirin → Non-selective COX Inhibitors → ↓ COX-I & ↓ COX-II.
2- Some e.g. Celecoxib & Rofecoxib → Selective COX-II inhibitors.

* Classification of Antipyretic Analgesics:

A) Non-Selective COX – Inhibitors:

1- Salicylates: Aspirin → Acetylation → Irreversible ↓ COX enzymes.
2- Anilines: Paracetamol → Selective ↓ CNS COX.
3- Pyrazolones: Phenylbutazone.
4- Propionic acid Derivatives: Naproxen.
5- Indols: Indomethacin.
6- Fenamates: Mefenamic acid.
7- Aryl Acetic Acid Derivatives: Diclofenac.
8- Nabumetone.
9- Oxicams: Piroxicam.

B) Selective COX-II Inhibitors:

Effective Anti-inflammatory & Anti-Rheumatic with Less Gastric & Renal toxicity.

1- *Celecoxib (Celebrex) 100 – 200 po*
2- *Rofecoxib (Vioxx) 12.5 – 25 – 50 mg po*
3- *Meloxicam (Mobic) 7.5 – 15 mg od po*
4- *Nimuselide (Sulide) 50 – 100 mg bid po*

Salicylates

★ Salicylic acid derivatives. Salicylic acid itself is very irritant.
★ They Include:

1- Salicylates for Systemic Use → Acetyl-salicylic acid (Aspirin), Na^+-Salicylate, Salicylamide & Diflunisal.
2- Salicylates for Local use → Salicylic acid & Methyl-salicylate.

* Kinetics:

1- Absorption:
a- Orally from upper G.I.T. → Acid pH ↑ absorption of salicylates.
b- *Better* absorbed fro stomach
But More from intestine (More surface area & time of contact).

2- Distribution:
a- All over the body & passes B.B.B. & placental barrier.
b- In plasma & tissues → Release of Salicylic acid.
c- Salicylic acid is 50-80% bound to plasma albumin → Displaces other drugs.

3- Hepatic Metabolism:
a- Mostly conjugation with Glucuronic acid & Glycine → Inactive Salicyluric acid.
b- Little → Oxidized → Active Gentesic acid.

4- Excretion:
a-Mainly renal. Some excretion in Saliva & Milk.
b- Alkalinization of urine → ↑ Renal excretion of Salicylates.

5- Plasma Half Life (t 1/2):
a- Aspirin (15 minutes) & Salicylic acid (3 – 6 hours).
b- Small dose → First Order Kinetics → Constant t ½.
c- Large dose → Zero Order Kinetics → ↑ t ½ with ↑ Dose.

* Dynamics of Salicylates:

Aspirin → Acetylation → Irreversible inhibition of *BOTH* COX-I & COX-II *BOTH* in C.N.S. & Periphery.

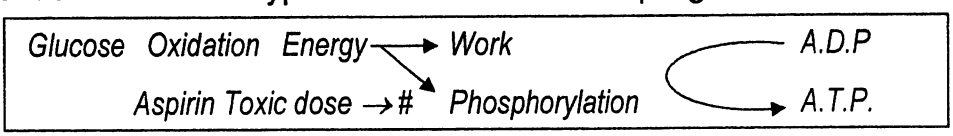
1- C. N. S.:

A) Analgesic:

1- Central mechanism → ↓ PG → ↑ Pain threshold especially in *Thalamus*.
2- Peripheral mechanism → ↓ PG → Sensitivity of Nociceptors (Pain receptors) to Histamine, Bradykinin & 5-HT → Anti-inflammatory.

B) Anti-Pyretic:

1- ↓ Synthesis of PG induced by IL & Other cytokines → Reset = Readjust Hypothalamic Heat Regulating Center → ↑ Heat Loss by:
   a- Peripheral V.D. → ↑ Heat loss by radiation.
   b- ↑ Sweating → ↑ Heat loss by evaporation.
   c- Mobilizes fluids from tissues to plasma.
2- Toxic Dose → Hyperthermia due to Uncoupling of Oxidative-Phosphorylation.



C) Toxic dose → Anti-GABA → Excitation

2-Anti-Iflammatory & Anti-Rheumatic:

1- ↓ PG synthesis (Directly & Indirectly) → ↓ Action of inflammatory mediators e.g. Histamine, Kinins, IL & INF:
   a- ↓ COX-II induced by inflammatory mediators → ↓ PG, PGI_2 & TXA_2.
   b-Aspirin Large dose → ↑ ACTH → ↑ Cortisol → Lipocortin → ↓ PLA-2 → ↓ Arachidonic acid → ↓ PG.
2- ↓ Kallikrein enzymes → ↓ Synthesis of Kinins → ↓ Pain, ↓ V.D. & ↓ Edema.
3- ↓ Migration of polymorphs & macrophages to site of inflammation.
4- Stabilization of lysosomes → ↓ Release of proteolytic enzymes → ↓ Cell death.
5- ↓ Hyaluronidase enzyme → ↓ Capillary permeability → ↓ Swelling, Edema & joint effusion
6- Aspirin Large dose → Uncoupling of Oxidative-Phosphorylation → ↓ ATP.

3- C. V. S.:

1- Therapeutic doses → No effect.
2- Toxic dose → V.D. → Hypotension.
3- In patients with active rheumatic carditis with heart failure (edema) → Aspirin (Acetyl-salicylic acid) is preferred than ***Na^+***-Salicylate (Na^+ → More edema).

4- Respiration & Acid / Base Balance:

1- *Small dose* up to 1 g (3 tablets aspirin) → No effect.
2- *Large Dose* > 5 g (> 15 tablets aspirin) in ***Adults*** → ↑ R.C. (Directly & through ↑ CO_2 production) → Hyperventillation → CO_2 wash → ***Respiratory alkaloisis*** → compensated by kidney → Excrete excess alkali.
In renal insufficiency → Decompansated alkalosis.
3- *Toxic dose* in ***Children*** → ***Metabolic acidosis*** due to impaired CHO metabolism
4- May precipitate ***bronchial asthma*** → ↓ COX → Shift to LOX pathway → LT.

5- G. I. T.:

1- Local → Release of Salicylic acid → irritation } - ***Pain, Ulcer & Bleeding.***
2- Systemic ↓ PG. → Hyperacidity } - ***Nausea & vomiting.***

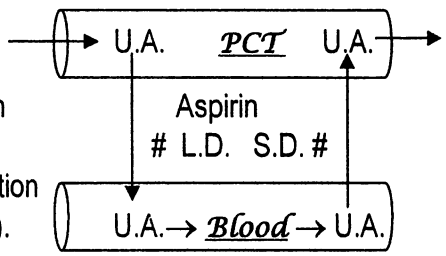
6- Liver:

1- *Hydrochloretic* → ↑ Water in bile.
2- ↑ Adrenaline → ↑ Hepatic *Glycogenolysis*.
3- *Hepatotoxic* (Reye's syndrome).

7- Kidney:

1- Aspirin → ↓ PG → ↓ Renal V.D. → Renal V.C. (Unopposed Angio-II & Noradrenaline) → ↓ R.B.F.
2- Large dose of salicylates → ***Nephropathy***.

8- Uric Acid Excretion:



1- *Small dose* of Aspirin (1-2 g /day) → ↓ Uric acid excretion by PCT → Hyperuricemia → *Worsens Gout*.
2- *Large dose* of Aspirin (> 5 g/day) → ↓ Uric acid reabsorption by PCT → *Uricosuric* → Treat gout. (Alkalinize the urine).

9- Uterus: ↓ PG → Uterine Relaxation → Tocolytic → Delays labor

10- Blood:

1- In inflammation, Aspirin → ↓ Elevated Erythrocytic Sedimentation Rate & ↓ Leucocytosis to normal (No leucopenia).
2- *Hypoprothrombinemia*: Aspirin Large Dose for long time → Coumarine like → Compete with Vit-K in liver → ↓ Synthesis of activated Prothrombin & factors VII, IX & X.
3- *↓ Platelet Aggregation*: Aspirin Small dose (75 – 150 mg) → Selective & Irreversible ↓ of Platelet Thromboxane Synthetase enzyme → ↓ TXA_2.
4- *Hemolysis (Idiosyncrasy)* in patients with Favism.

11- Endocrine:

1- ↑ Hypothalamus → ↑ ACTH → ↑ Adrenal cortex → ↑ Cortisol.
2- ↑ Adrenal medulla → ↑ Adrenaline.
3- Displaces T-3 & T-4 from plasma proteins → ↑ Their free form → ↓ T.S.H.

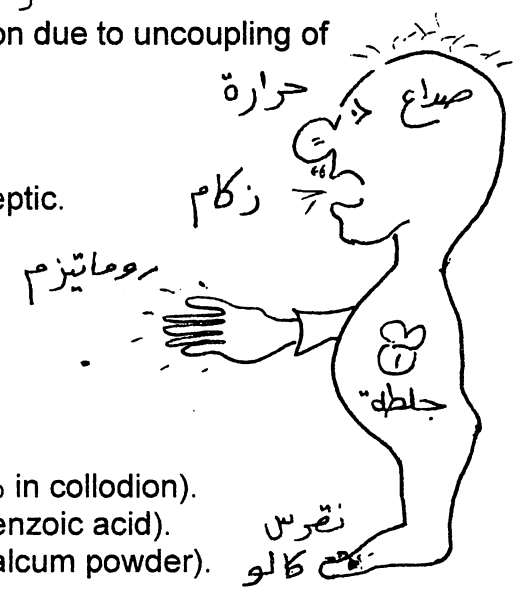
12- Immune response: ↑ Cortisol → ↓ Ag / Ab reaction.

13- Metabolism:

1- *Carbohydrates*:
   a- Moderate dose → Insulin like → Hypoglycemia.
   b- Large dose → ↑ Adrenaline & ↑ Cortisol → Hyperglycemia.
2- *Fat* → Lipolysis & ketosis (Toxic dose in children).
3- *Protein* → Catabolic → -ve Nitrogen balance.

} Large Dose → ↑ Cortisol

4- *↑B.M.R.* → ↑ O_2 consumption & ↑ CO_2 production due to uncoupling of Oxidative/Phosphorylation.



14- Local Actions:

1- *Salicylic Acid* → Keratolytic, Fungistatic & Anti-septic.
2- *Methyl-Salicylate* → Irritant.

*Therapeutic Uses of Salicylates:

A) Local Uses:

1- Salicylic acid:
   a- Keratolytic in corns & warts (Salicylic acid 20% in collodion).
   b- Fungistatic in Tinea of Skin (Salicylic acid + Benzoic acid).
   c- Anti-septic in Hyperhidrosis (Salicylic acid + Talcum powder).

2- Methyl-Salicylate (*Oil of Wintergreen*) → Counter-irritant in Arthritis & Myositis.

B) Systemic Uses:

1- *Anti-pyretic* → Non-specific & Non-causal.
2- *Analgesic* in Mild superficial pains e.g. Headache, Toothache, myalgia, arthralgia & Neuralgia. Effective in dysmenorrhea (PG) but may ↑ Bleeding.
3- *Common cold* → Treat Fever, headache, muscle and joint pains.

*Uses 1, 2 & 3: Dose 1, 2 or 3 tablets 1, 2 or 3 times/day.

4- Rheumatic fever (Arthritis) → 6-12 g/day (1-2 g/4 hours after meal) Treat fever, arthritis, ↓ ESR, ↓ Leucocytosis. *Not* effective in Carditis, Chorea or Cutaneous nodules.
5- Rheumatoid arthritis 5 -6 g / day in divided doses.
6- Chronic gout 5-8 g/day (Alkalinize urine & ↑ Fluid intake).

*Uses 4, 5 & 6: Dose 6 g / day (1 g / 4 hours) After meals.

7- Antiplatelet (75-150 mg/day) → Prophylaxis against thrombo-embolic diseases.
8- Prophylaxis against cancer rectum & colon, Alzheimer's disease, Radiation-induced diarrhea & Cataract.

*Preparations:

1- Aspirin (Acetyl-Salicylic Acid) 0.3 – 1 g → Simple tablet, Soluble tablet, Micronized, Effervescent & Buffered (Aspirin + Antacid).

2- Sodium Salicylate (0.6 – 1.2 g) Enteric coated tablet. 

3- Diflunisal *(Doloban & Dolozal): 250 – 500 mg bid po*
   a- More analgesic *But Not* Antipyretic.
   b- More Anti-inflammatory & Anti-rheumatic.
   c- Uriucosuric.
   d- Less Anti-platelet & Less gastric irritation.

4- 5-Aminosalicylic acid (Sulfasalazine, Salazopyrine) → LTB-4 receptor blocker → Anti-inflammatory → PO in Inflammatory Bowel Syndrome eg Ulcerative colitis

*Adverse Effects & Toxicity of Salicylates: (ASHGAR TIN)

1- Acute Toxicity:

- ♦ Salicylates have a high therapeutic index (wide safety margin).
- ♦ Toxic dose > 200 mg / kg.
- ♦ Children are more liable for toxicity.

Manifestations:

1- Hyper-reflexia, excitation, convulsions *then* coma.
2- Hyperpyrexia, Hyperventillation & Hyperhidrosis → Dehydration.
3- Hyperacidity & irritation → Nausea, Vomiting, Pain, Ulcer & Bleeding.
4- Hyperglycemia.
5- Hypoprothrombinemia.
6- Hypotension.
7- Acid/Base imbalance.

Management:

1- Symptomatic.
2- Stomach wash by Sodium bicarbonate.
3- ↑ Urinary excretion: Alkalinization of urine + Forced diuresis (I.V. fluids, Diuretics). Hemodialysis may be needed
4- Anti-convulsants.
5- Cooling → Ice bags.
6- Correct Dehydration & Acid/Base imbalance.
7- Vit K + Fresh blood transfusion.

2- Salicylism: Large dose for Long time → Tinnitus, blurring of vision, GIT upset, irritability & hyperventilation. Reversible after stopping salicylates.
3- Hypoprothrombinaemia → Bleeding tendency.
4- G.I.T. irritation → Nausea, voting, pain, ulceration & bleeding.
   *PG e.g. **Misoprostol** is useful in treatment of NSAID-induced peptic ulcer.*
5- Allergy (Hypersensitivity) → Rash, urticaria, angio-edema & Bronchial asthma. Bronchial asthma may be Ag/Ab reaction or ↓ COX → Shift to LOX → ↑ LT. ***LOX-inhibitors*** *(Zileuton) &* ***Cysteinyl LT-1 receptor blockers*** *(Montelukast, Zafirlukast & Pranlukast) are useful in Aspirin-induced asthma.*

6- **R**eye's syndrome: Aspirin in some children with viral infection (e.g. Influenza or Chicken pox) → Encephalopathy & Hepatotoxicity.
7- **T**eratogenicity → Cardiac septal defect.
8- **I**diosyncrasy → Hemolysis in patients with Favism.
9- **N**ephropathy.

*Contraindications of Salicylates:

1- Allergy to salicylates.
2- Idiosyncrasy (Favism).
3- Bleeding tendency
4- Bronchial asthma.
5- Peptic ulcer
6- Pregnancy
7- Gout:
   a- Small dose → Worsens gout.
   b- Antagonizes other uricosuric agents.
8- Children:
   a- More susceptible for adverse effects & toxicity.
   b- Reye' syndrome.

*Drug Interactions of Salicylates:

1- Salicylates → **Displace** other drugs from plasma proteins eg Oral anticoagulants & Oral hypoglycemica → Toxcity.
2- Salicylates **antagonize**:
   a- Other uricosuric agents.
   b- Other anti-inflammatory drugs.
   c- Antihypertensive effect of β-Blockers, ACE inhibitors & Diuretics.
3- NSAID, Corticosteroids & Alcohol → ↑ **Ulcerogenic** effect of Salicylates.
4- Phenobarbitone → ↑ **Metabolism** of Salicylates.
5- Alkalinizers of urine e.g. $NaHCO_3$ → ↑ **Renal** excretion of Salicylates
   Acidifiers of urine e.g. Ammonium chloride → ↓ **Renal** excretion of Salicylates.

2- *Aniline Derivatives*

- Phenacetin (Active) —*Liver*→ Paracetamol (Active).
- Paracetamol (*Acetaminophen*)

*Kinetics:

1- Well absorbed orally.
2- Hepatic Metabolism:
   a- 95% → Conjugation with Glucuronic acid & Sulfate → Inactive metabolite.
   b- 5% → CYP 450 → N-Acetyl-P-Benzo-Quinone (NABQ) → *Toxic* Metabolite → Conjugation with Glutathione-SH → Non-Toxic.
   c- Large dose of Paracetamol → Depletion of Glutathione-SH → Accumulation of NABQ → Hepatotoxicity & Nephrotoxicity.
3- Excreted in urine: Mostly as metabolites & Only 5% unchanged.
4- t ½ = 2 - 3 hours.

*** Dynamics of Paracetamol:**

1- ↓ *COX-3* **in C.N.S. Mainly** → Anti-pyretic Analgesic → As potent as Aspirin.
2- Almost **No** peripheral Action → Almost **No** Anti-inflammatory & Almost **No** effect on → Respiratory, C.V.S., Platelet aggregation, Gastric acidity or Uric acid.

*** Therapeutic uses of Paracetamol:**

Paracetamol *(+ Methionine) 250 – 5 00 mg (Paramol, Abimol, Pyral, Tylenol) Tablets, Capsules, Syrup, Drops & Suppository.*

As Antipyretic Analgesic (1/2 – 1 g) especially in patients who can not tolerate aspirin e.g. → Allergy to Aspirin, Bronchial asthma, Children with viral infection, Bleeding tendency, Peptic ulcer & Gout.

*** Side Effects & Toxicity:**

1- **Toxic dose of Paracetamol** (> 10 g in Adults & 4 g in Children) → Depletion of Glutathione-SH → **Hepatotoxic & Nephrotoxic** → Fatal.
Management: I.V. N-Acetylcysteine (Rich in S-H) + Oral Methionine.
2- **Phenacetin** → Nephrotoxicity + Met Hb & Hemolysis → Obsolete.
3- Allergy (Hypersensitovity).

NB) Benotrylate *(Benoral):*

1- Ester of Aspirin + Paracetamol
2- Anti-pyretic, Analgesic & Anti-inflammatory → Similar to Aspirin.
3- Less gastric irritation than Aspirin.

3- *Pyrazolone Derivatives*

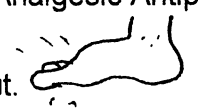
1- Phenylbutazone *(Butazolidine):*

***Kinetics:**

1- Well absorbed Orally, Rectally & Parenterally.
2- Distributed All-over the body
3- Highly bound to plasma proteins (98%) → **Displaces** other drugs.
4- Hepatic Metabolism → **Active Metabolites**:
a- **Oxyphenbutazone** *(Tandril)* → Potent & Long acting → Anti-inflammatory
b- **γ-HydroxyPhenylbutazone** → Potent & Short acting → Uricosuric.

*** Dynamics of Phenylbutazone:**

1- ↓ **COX (↓ Peripheral** > Central) → **Anti-inflammatory** > Analgesic Antipyretic.
2- Uricosuric.



* **Used** as Anti-inflammatory e.g. Arthritis & Acute Gout.

*** Adverse Effects:**

1- CNS → Nervousness & Vertigo
2- Allergy → Skin rash & Bronchial asthma
3- GIT → Irritation & Peptic ulcer
4- Liver & Kidney damage
5- Teratogenic
6- Bone marrow inhibition → Agranulocytosis ☠
7- Na^+ & Water retention → Edema & ↑ Bl.p.
8- Displaces other drugs e.g. Oral Anticoagulants & Oral Hypoglycemics from plasma proteins.

*** Contraindications:**

1- Extremities of Age.
2- Allergy & Asthma
3- Peptic ulcer
4- Liver & Kidney diseases
5- Pregnancy
6- Heart failure & Hypertension

2- Azapropazone (Apazone, *Prolixan*):

Similar to Phenylbutazone *But*:

1- Not metabolized → Long t ½ = 12 hours.
2- Less adverse effects.

3- Dipyrone (Metamizd, Novalgin)

1- Antipyretic Analgesic.
2- Related to Phenylbutazone → May cause Agranulocytosis.

NB) All The Following NSAID:

1- ↓ Both Central & Peripheral Cyclo-oxygenase enzymes Both COX-1 & COX-2:
   a- Antipyretic Analgesic.
   b- Anti-inflammatory & Anti-Rheumatic.
2- Not uricosuric.
3- Displace other drugs from plasma proteins.
4- Gastric irritation.
5- Contraindicated in Peptic Ulcer & Bronchial asthma.
6- Uses:
   a- Antipyretic analgesic.
   b- Anti-Inflammatory e.g. Arthritis, myositis & Acute Gout.
   c- Colic e.g. Dysmenorrhea.

4- Indol Derivatives:

1- Indomethacin (Indocid):

1- **Very Potent** ↓ COX Both Central & Peripheral BOT COX-1 & COX-2.
   a- Potent Antipyretic analgesic.
   b- Potent Anti-inflammatory & Anti-Rheumatic.

2- **Not** Uricosuric.

3- **Uses**:
   a- To close Patent Ductus Arteriosus in neonates with normal great vessels.
   b- Arthritis, Myositis & Acute gout.
   c- Dysmenorrhea & Premature labor.

4- **Enterohepatic** circulation

5- **Adverse Effects** &

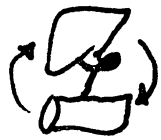
a- CNS → Confusion & Psychosis
b- Corneal opacity & Blurred vision
c- Allergy & Bronchial asthma
d- GIT → Irritation & Peptic ulcer
e- Liver & Kidney damage
f- Teratogenic
g- Bone marrow inhibition → Leucopenia

Contraindications

a- Psychosis, Epilepsy & Parkinsonsim
b- Allergy & Asthma
c- Peptic ulcer
d- Liver & Kidney disease
e- Pregnancy
f- Extremities of age

h- Displaces other drugs from plasma proteins → ↑ Their free form → ↑ Their activity & toxicity.

2- Sulindac *(Hi-Dac, Rudac): 150 – 200 mg tablets*



1- Similar to Indomethacin *But* less Potent & Less Toxic.
2- Sulindac → *Prodrug* → Sulindac sulfide → Active Metabolite.
3- *Entero*-Heptic circulation.
4- **↓ BOTH COX & LOX**.
5- **Little effect on renal PG** → Allowed in patients with mild renal insufficiency.
6- *Anti-oxidant*.
7- **Uses** (100-200 mg): Arthritis, Acute Gout & Cataract.

5- Phenyl-Acetic Acid Derivatives

1- Diclofenac (Na → Voltaren or K → Cataflam):

1- **Kinetics**:
a- Absorbed orally, Rectally & I.M.
b- Distributed All-over the body.
c- ***Concentrated in synovial fluid 4 times > plasma***
d- Rapid Hepatic Metabolism → ***Short*** t ½.

2- **Dynamics**:
a- ↓ COX **Both** Central & Peripheral **Both** COX-1 & COX-2
b- ↑ **Incorporation** of Arachidonic acid into Triglycerides → ↓ Both PG & LT.

3- **Uses**: 12.5-25-50-75-100 mg
Tablets (Enteric coated, sustained release, dispersible), capsules, suppository, I.M., skin gel & Eye drops.
a- Inflammations e.g. Arthritis, Myositis & Acute Gout.
b- Colic e.g. Dysmenorrhea.
c- Eye drops to treat ocular inflammations e.g. Postoperative.

4- **Adverse Effects**:
a- GIT irritation (Used as Enteric coated tablets & Taken after meals).
b- Hepatotoxicity → ↑ Serum transaminases.

2- Aceclofenac *(Bristaflam) 100 mg tablets*

3- *Etodolac (Etodine)* 200 – 300 mg capsules

4- Ketorolac *(Ketolac) 10 mg tablets*

5- Tolmetin *(Tolectin) 200 mg capsules* → Short t ½ = 1 hour.

NB) Nabumetone:

1- *Ketone Prodrug* → Active metabolite → Acetic acid derivative.
2- *↓ COX-2 > COX-1* → Less adverse effects on Stomach & Kidney.
3- *Long t ½* = 24 hours.

6- Oxicams

1- **Piroxicam** *(Felden) 10–20 mg* → Entero-Hepatic circulation → Long t ½ = 45 hs

2- **Tenoxicam** *(Epicotil) 20 mg*

3- **Meloxicam**(Mobic, Mbitil) 7.5 – 15 mg tablets → Selective COX-2 inhibitor

7- Propionic Acid Derivatives

1- **Naproxen** (Naprosyn) 250 – 500 mg tablets, suppository, gel & Parenteral:
   a- Stronger 20 times > Aspirin
   b- Long t ½ = 14 hours

2- **Tiaprofenic acid** *(Surgam) 100-200-300 mg tablet & suppository*

3- **Ibuprofen** *(Brufen) 100 – 600 mgTablet, Pack & suppository*

4- **Ketoprofen** *(Ketofan) 12.5 – 200 mg Tablet, capsule, suppository & Parenteral*

5- **Fenoprofen** *(Nalfon)*

6- **Flurbiprofen** *(Froben) 50 mg tablets*

8- Fenamates

1- **Flufenamic Acid** & **Mefenamic Acid** *(Ponstan) 250 – 500 mg Cap. & Syrup*
2- Anti-pyretic & Anti-inflammatory
3- *Mefenamic acid* has in addition an *Analgesic* effect.
4- **Not** used in Children or Pregnancy or More than a weak.
5- May cause severe *diarrhea*.

9- Selective COX-II Inhibitors:

Effective Anti-inflammatory & Anti-Rheumatic with Less Gastric & Renal toxicity.

1- Celecoxib *(Celebrex) 100 – 200 po*

2- Rofecoxib *(Vioxx) 12.5 – 25 – 50 mg po*

3- Meloxicam *(Mobic) 7.5 – 15 mg od po*

4- Nimuselide *(Sulide) 50 – 100 mg bid po*

NB) Non-Steroidal Anti-inflammatory Drugs (NSAID)

* Mechanism of Action of NSAID :

They inhibit COX → ↓ Synthesis of prostaglandins (PGs), Prostacyclin (PGI_2) & Thromboxane A_2 (TXA_2).

* Types of Cyclo-Oxygenase Enzymes (C.O.X.):

A) COX-1: Constitutive → Physiological

1- Stomach ↓ HCl (Prevent peptic ulcer).
2- Kidney → Renal VD.

B) COX-2: Inducible by inflammation → Pathological

Infection → Toxins → IL-1 & TNF → ↑ COX-II → ↑ PG → Inflammation

1- C.N.S.:
   a- Hypothalamus → HRC → Fever. b- Thalamus → Pain
2- Periphery → Inflammation:
   a- Sensitize Nociceptors to Histamine, bradykinin & 5-HT → Pain.
   b- Potentiate effect of histamine & bradykinin →
      - V.D. → Redness & hotness.
      - ↑ Capillary permeability → Edema.
   c- Enhance other cytokines

NB) Drugs & COX Enzymes:

1- Most of NSAID e.g. Aspirin → Non-selective COX Inhibitors → ↓ COX-I & ↓ COX-II.
2- Some e.g. Celecoxib & Rofecoxib → Selective COX-II inhibitors.

* Common Actions of NSAID:

1- Analgesic:

a- ↓ PGs centrally → ↑ Pain threshold specially in the thalamus.
b- ↓ PGs peripherally → ↓ Sensitization of nociceptors by histamine, serotonin & bradykinin.

2- Antipyretic:

a- ↓ Synthesis of PGE_2 induced by interleukin-1 that is released by bacterial toxins → Reset hypothalamic HRC → ↑ Heat loss.
b- ↑ Heat loss by: Cutaneous VD, ↑ Sweating & mobilizes tissue fluids to blood.

3- Anti-inflammatory & Anti-rheumatic:

↓ COX-2 induced by inflammation → ↓ PGs, PGI_2 & TXA_2 → ↓ action of inflammatory mediators e.g. bradykinin, histamine & cytokines (Interleukins & interferons).

4- C.V.S.:

a- Closure of Ductus arteriosus.
b- Antiplatelet → Anti-thrombotic.
c- Prevent V.D. & ↓ Bl.p. induced by PG e.g.: Niacin & Systemic Mastocytosis.

5- Respiration → Bronchial asthma

6- G.I.T.:

a- Irritation & Ulceration → Occult blood in stool → Anemia.
b- Prevent cancer colon & polyps.

7- Liver → ↑ Transaminases

8- Kidney → ↓ R.B.F. & ↓ G.F.R. → Sodium & Water retnstion.

9- Anti-Gout :

a- *Acute gout*: Anti-inflammatory & Analgesic effects e.g. Indomethacin.
b- *Chronic gout*: Uricosuric effect e.g. Salicylates LD & Phenylbutazone.

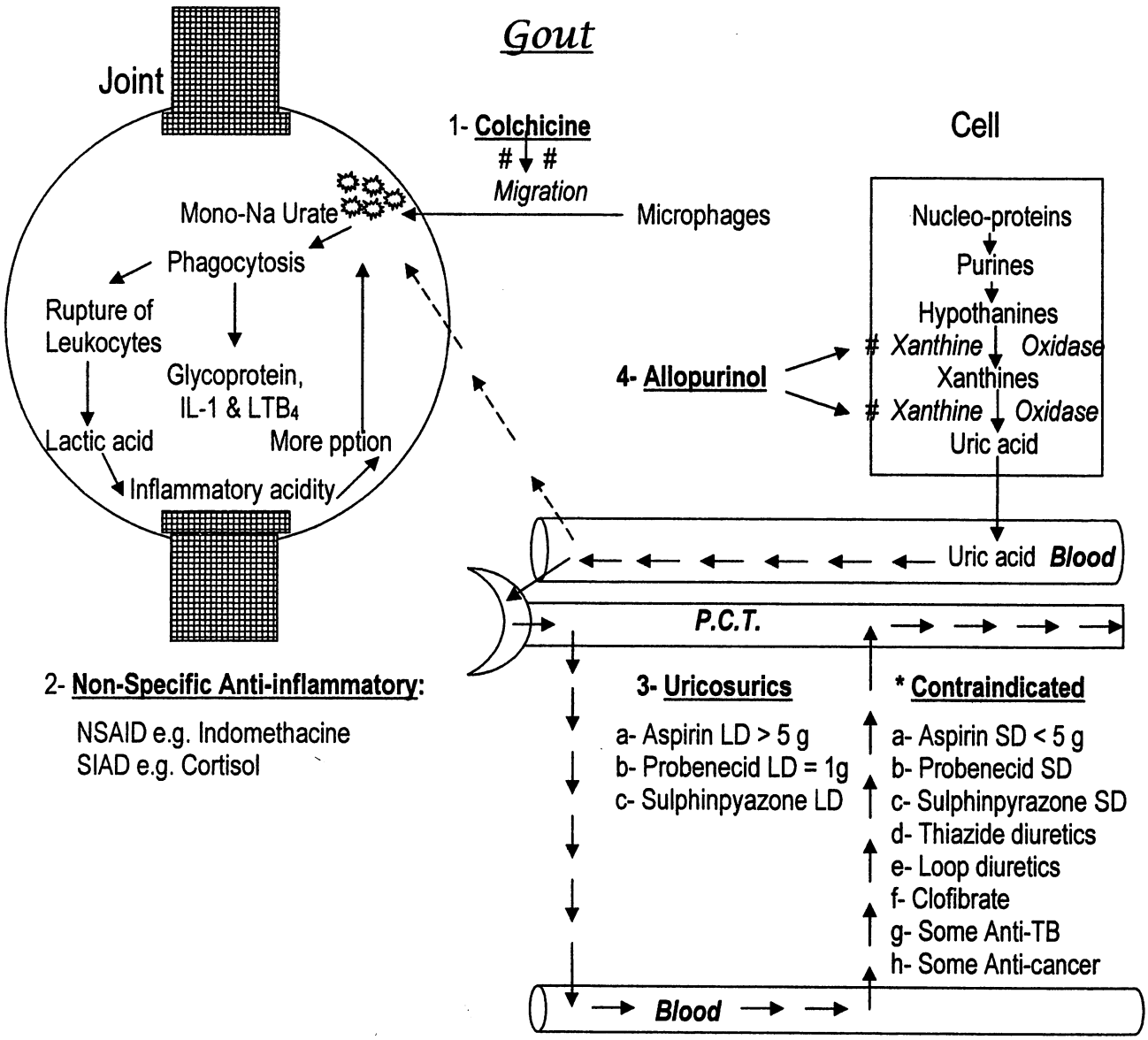
10- Uterus → ↓ PG-induced uterine contractions → **Tocolytic**

a- Treat dysmenorrhea.
b- In Pregnancy:
- Prevent premature labor.
- Premature closure of ductus arteriosus.

11- Displace other drugs from plasma protein binding sites.

* Common Side Effects of NSAID:

1- **Allergy** (Hypersensitivity) reaction.
2- **Idiosyncrasy**: Aspirin and phenacetin → Hemolysis in patients with Favism.
3- **CNS**:
   a- Phenylbutazone → Nervousness & vertigo.
   b- Indomethacin → Confusion and convulsions.
4- **Eye**: Indomthacin → corneal opacities and blurring of vision.
5- **CVS and Blood**:
   a- Phenylbutazone → Fluid rertension → Oedema & hypertension.
   b- Bone marrow inhibition e.g. phenylbutazone.
   c- Premature closure of ductus arteriosus.
6- **Respiration**→ Bronchial asthma:
   a- Allergic reaction.
   b- ↓ COX → Shift arachidonic acid to lipooxygenase pathway → ↑ Synthesis of leukotrienes → SRS-A.
   c- *Management*:
      - ↓ Synthesis of LT: 5-Lipo-oxygenase inhibitor e.g. Zileuton.
      - LT-1 receptor blockers e.g Montelukast.
7- **Gastric** irritation & ↑ HCl → Nauseam Vomiting, ulcer and bleeding.
   Management of peptic ulcer by PG analogues e.g. Misoprostol.
8- **Hepatotoxicity** e.g. Paracetamol.
9- **Nephropathy**:
   a- Toxic effect e.g. Paracetamol & Phenacetin.
   b- ↓ PG → Renal VC → Analgesic nephropathy.
10- **Uterus** → Teratogenecity.
11- **Specific**:
   a- *Salicylism* induced by large dose of salicylates.
   b- *Reye's* syndrome induced by Aspirin in infants infected with viral infections.
12- **Acute toxicity** e.g. by Aspirin (ASHGAR TIN).



Treatment of Gout

A) Acute Attack:

1- ***Colchicine*** specific drug of Choice.
2- *Non-Specific Anti-inflammatory drugs*:
   a- N.S.A.I.D. e.g. Indomethacin & Naproxen.
   b- S.A.I.D. e.g. A.C.T.H., Cortisol or Prednisolone

B) Prophylaxis (Between Attacks):

Drugs ↓ blood level of uric acid (< 6 mg/100 blood)

1- ***Uricosurics*** → ↑ Urinary excretion of uric acid:
   a- **Aspirin** L.D. > 5 g /day
   b- **Probenecid** L.D. > 1 g / day
   c- **Sulphinpyrazone** L.D. 100 mg tds
   d- **Benzbromarone** 40 -80 mg / day
2- ***Xanthine-Oxidase Inhibitors*** → ↓ Synthesis of uric acid e.g. **Allopurinol.**

1- Colchicine & Demecolcine:

Natural plant alkaloid

* Actions:

A) Anti-Gout Effect:

1- Specific drug of *CHOICE* in *Acute Attack of Gout*.
2- ***NOT*** effective in other types of arthritis.
3- ***NOT*** affect uric acid synthesis or excretion or blood level.
4- It binds to Microtubular protein (*Tubulin*) of P.M.N.L.:
   a- ↓ Migration of P.M.N.L. to joints →
   b- ***NO*** Phagocytosis of Mono-sodium urate crystals →
   c- ***NO*** Ruptures of leukocytes →
   d- ***NO*** release of lactic acid → ***NO*** Inflammatory acidity.
   e- ***NO*** release of chemotachtic factors e.g. Glycoproteins, IL-1 or LTB_4] ***NO*** further pption of urate crystals

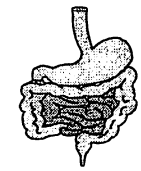
B) Anti-Mitotic Effect → Inhibits cell division.

* Therapeutic Uses:

1- Acute attacks of gout (Maximum dose 6 mg):
   a- Orally: 1 mg then ½ mg / 2 hours till relief of pain or appearance of toxicity (Diarrhea).
   b- I.V.: 2 mg then ½ mg / 6 hours.
2- Prophylaxis of Gout: 1 – 2 mg / week orally.
3- Prophylaxis of Familial Mediterranean Fever *(Polyseoritis)*.
4- Liver cirrhosis.
5- Psoriasis.

* Adverse Effects:

1- Reversible alopecia.
2- G.I.T. → Nausea, vomiting & *Diarrhea*.
3- Hepatotoxicity & Nephrotoxicity → Hematuria & Oliguria.
4- Myopathy.
5- Bone marrow inhibition.



2- Probenecid (Benemid):

1- Large dose > 1 g / day → ↓ Uric acid reabsorption from P.C.T. → **Uricosuric**.
   This effect is antagonized by Aspirin.
2- Small dose < 1 g / day → ↓ Uric excretion in P.C.T. → **Worsens gout**.
3- ↓ Active tubular excretion of weak acid drugs:
   a- Penicillin & Para-Amino-Salicylic acid (P.A.S.A., Anti-TB) → ↑ Their duration of action.
   b- Thiazide & loop diuretics → Antagonize their diuretic effect.
4- *Adverse Effects*:
   a- Formation of renal urate stones → Avoid by Alkalinization of urine + Plenty fluid intake.
   b- G.I.T. disturbances.
   c- Allergy.

3- *Sulphinpyrazone (Anturane):*

1- Derivative of Phenylbutazone.
2- ***Potent Uricosuric*** BUT **NOT** Analgesic, **NOT** Anti-inflammatory & **NO** Na^+ & H_2O retention
→ *Useful in Prophylaxis of Chronic gout: Alkalinize the urine + Plenty fluid intake.*
3- ***↓ Platelet aggregation*** → *Useful in Prophylaxis of Thrombo-embolic diseases.*
4- Large dose → Gastric irritation → Avoid in Peptic ulcer.
5- *Uses*: 100 mg t.d.s. p.o.

4- *Benzbromarone;*

Potent Uricosuric (40 – 80 mg / day p.o.) → **No** paradoxical hyperuricemia.

5- *Allopurinol (zyloric):*

1- Allopurinol is metabolized by *Xanthine Oxidase enzyme (XOE)* → Alloxanthine (Oxipurinol)
2- Both Allopurinol & Alloxanthine → Occupy & ↓ X.O.E. → ↓ Synthesis of uric acid.
3- It has **NO** effect on renal excretion of uric acid.
4- Therapeutic Uses → ***Hyperuricema & Chronic Gout*** specially in:
a- Gouty nephropathy & urate renal stones.
b- Associated with the use of Anti-Cancer drugs.
c- If uricosuric drugs are ineffective or contraindicated.
5- Adverse Effects:
a- Acute attacks of gout during initiation of treatment → Add Colchicine prophylactically.
b- C.N.S. → Headache & psychological changes.
c- Allergy.
d- G.I.T. disturbances.
e- Hepatomegaly.
f- Leucopenia.
g- Better avoided in children & during lactation.
h- Drug Interaction → ↓ Metabolism of Probenecid & 6-Mercaptopurine (Anti-cancer) → Toxicity.

N.B)

1- With the use of **Uricosurics**:
a- Alkalinize the urine + Plenty fluid intake.
b- **Do NOT** use Aspirin → Antagonizes uricosuric agents.
2- **Coffee & Tea** are **NOT Contraindicated**.
They are Methyl-xanthines → Methyl-uric acid → Soluble.

3- Avoid **red meat & liver** → Nucleo-proteins → Xanthines → Uric acid → Worsen gout.
4- Drugs **Contraindicated:**

a- Aspirin S.D. < 5 g / day.
b- Probenecid S.D. < 1 g / day.
c- Sulphinpyrazone S.D.
d- Diuretics e.g. Thiazides, Loop & Acetazolamide. Diazoxide, a V.D. →Thiazide derivative
e- Clofibrate → Treat hyper-lipoproteinemia.
f- Some Anti-TB e.g. Pyrazinamide & Ethambutol.
h- Some Anti-cancer drugs.

Anti-Inflammatory & Anti-Rheumatic Drugs

I- Steroidal Anti-Inflammatory Drugs (SAID): e.g. Prednisolone.

II- Non-Steroidal Anti-Inflammatory Drugs (NSAID):

A) Rapidly Acting Anti-Rheumatic Drugs (RA-ARD):

- Almost All Antipyretic Analgesics *Except* Paracetamol.

B) Slow Acting Anti-Rjeumatic Drugs (SA-ARD) = Disease Modifying Anti-Rheumatic Drugs (DM-ARD):

1- **Leflunomide** (Avara) 10 – 20 mg Orally:

a- Immuno-modulator.

b- ↓Di-hydro-orotate dehydrogenase → ↓ Pyrimidine synthesis → ↓ T-lymphocytes

2- **Chloroquine & Hydroxy-Chloroquine** *(Hydroquine)* 200 mg orally:

a- Anti-malarial.

b- ↓ T-lymphocytes & Stabilizes the lysosomes.

3- **Gold Salts** *e.g.* **Sodium Auro-thiomalate** *(Myocrisin) 50 mg* I.M. / weak.

a- ↓ Phagocytosis & ↓ Lysosomal enzymes.

b- Adverse Effects → Dermatitis, Liver & Kidney damage & ↓ bone marrow.

4- **D-Penicillamine** *(Artamine) 250 mg* Orally:

a- Chelates copper.

b- Modifies immunoglobulins.

5- **Sulfasalazine (Salazopyrine)**:

a- Split by colon bacteria → 5-Aminosalicylic acid → Anti-LTB_4 → # Chemotaxis

b- Useful orally in:

- Chronic inflammatory Bowel diseases (IBD) e.g. Ulcerative colitis
- Rheumatoid arthritis.

6- **Immuno-suppressants** e.g. Anti-metabolites such as Methotrexate.

7- **Immuno-stimulants** e.g. *Levamisol* (Anti-helminthic).

NB) **Colchicine** has an anti-inflammatory effect in especial cases only:

1- Acute gouty arthritis.

2- Familial Mediterranean fever (Polyseoritis).

Treatment of Parkinsonism

1-***Parkinsonism*** is a disease of the ***basal ganglia*** characterized by bradykinesia, rigidity, static tremors, postural instability, salivation & depression.

2-***Parkinsonism*** is due to degeneration of the Nigrostriatal dopaminergic system = Hyperactive cholinergic system.

3-***Aim of treatment*** is to restore the balance between Dopamine (D_2) / A.Ch (M).

Anti-Parkinsonian Drugs

A) Drugs ↑ Dopaminergic Activity:

1- **Levo-Dopa** (L-DOPA) ± Peripheral Dopa Decarboxylase Inhibitors e.g. Carbidopa.
2- **COMT-Inhibitors** e.g. Tolcapone & Entacapone.
3- **MAO-B Inhibitors** e.g. Selegyline (Deprenyl).
4- **Direct Dopamine Agonists**:
   a- *Ergoilines*: Bromocriptine, Pergolide & Lisuride.
   b- *Non-Ergot*: Pramipexole & Ropinirole.
5- **Amantadine**.

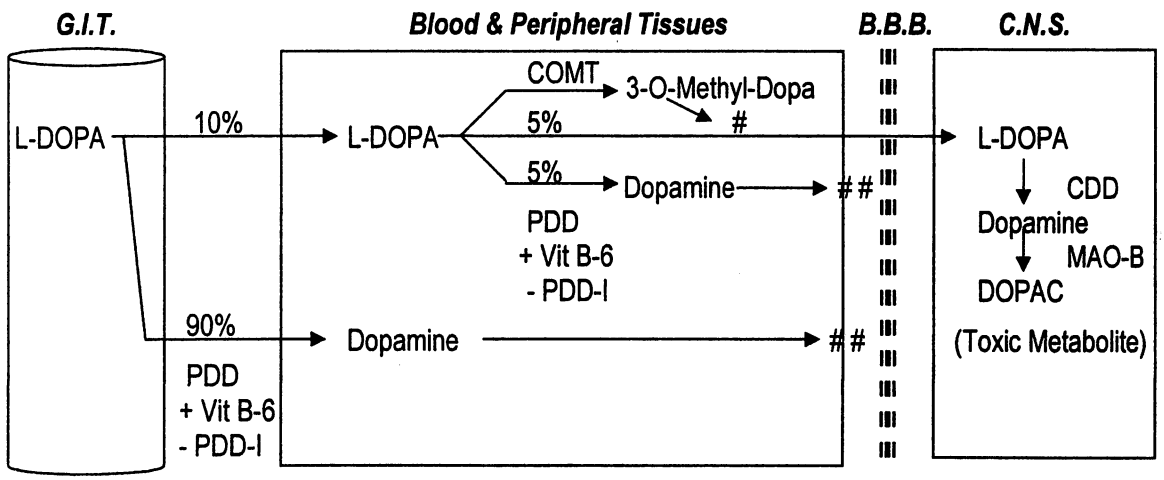
B) Anti-Cholinergic Drugs:

1- **Parasympatholytics**:
   a- *Natural Belladonna Alkaloids*: Atropine & Hyoscine.
   b- *Synthetic Atropine Substitutes* e.g. Benztropine.
2- **Anti-Histaminics**: Diphenhydramine.
3- **Phenothiazines**: Ethopropazine.

1- Levodopa (l-DOPA)

*Anti-Parkinsonian Effect:

1- Prodrug $\xrightarrow{\text{Central Dopa Decarboxylase (CDD)}}$ Dopamine → ↑ D_2-receptors.
2- Best results are obtained in the first few (3-4) years.
3- It treats all manifestations especially Bradykinesia > Tremors.



* Pharmacokinetics of L-DOPA:

1- L-DOPA is absorbed from intestine by active process.
Absorption is affected by gastric emptying, pH and presence of food specially proteins. Dietary aminoacids may compete with its absorption.
3- > 95% of ingested L-DOPA (90% in gut mucosa & 5% in blood and peripheral tissues) are metabolized by Peripheral Dopa-Decarboxylase enzyme (PDD) into Dopamine that cannot pass the BBB.
4- Part of L-Dopa $\xrightarrow{COMT}$ 3-O-Methyl-Dopa → Compete with L-Dopa for uptake by CNS.
5- Only < 5% of ingested L-DOPA can escape metabolism and passes the BBB by active process. There is competition with some aminoacids.
6- In CNS l-dopa $\xrightarrow{Central\ Dopa\ Decarboxylase}$ dopamine.
7- Fate of Dopamine:
a- Dopamine $\xrightarrow{CNS\ MAO\text{-}B}$ Di-Hydroxy-Phenyl-Acetic Acid (DOPAC), Toxic → Urine
b- Dopamine $\xrightarrow{MAO\ \&\ COMT}$ Homovanilic acid → Urine.
8- t ½ = 1 – 3 hours.

* Interactions of L-Dopa:

A) Desirable = Favorable:

1- ***Peripheral Dopa Decarboxylase Inhibitor*** (Can NOT pass BBB) → ↓ Dose of L-DOPA → ↓ Peripheral Adverse effects *But* ↑ Central Adverse effects. *Examples*:
a- **Carbidopa** (10 & 25 mg) + l-DOPA (100 & 250 mg)"1:10"= ***Sinemet*** bid or tds
b- **Benserazide** (25 mg) + l-DOPA (100 mg) "1:4" = ***Madopar.***
2- MAO-B inhibitor e.g. ***Selegiline (Deprenyl)***.
3- COMT-Inhibitors e.g. ***Tolcapone*** & ***Entacapone***.
4- Anti-Muscarinic drugs e.g. ***Benztropine***.

B) Undesirable = Unfavorable:

1- **Dopamine$_2$-receptor blockers**:
a- *Neuroleptics* e.g. phenothiazines & Butyrophenones.
b- *Anti-emetics* e.g. Metoclopramide.
2- **Pyridoxine (Vit B_6)** → ↑ PDD → Accelerates peripheral decarboxylation → Dopamine.
3- **Non-selective MAO-I** → Severe hypertension.

* Adverse Effects of L-DOPA:

1- **Fluctuation in Response:**
a- At first there is increased sensitivity to l-DOPA → Good response *then* ↓ response →
b- Wearing-off
c- End-of-dose Akinesia.
c- On-off phenomena.
} - Formation of DOPAC → H_2O_2 → Free radicals → Destroy Dopamine storage vesicles → Rapid ↑ then rapid ↓ of Dopamine level in CNS.

Management:
a- Increase the frequency of intake of l-DOPA, every 2 Hs.
b- Use of slow release preparations (Sinemet CR).
c- Add long acting direct dopamine agonists e.g. Bromocriptine & Pergolide.
d- Drug-holiday for 3-21 days.

2- C.N.S.:
a- Dyskinesias e.g. chorea, athetosis & tremors. Reduce dose of l-Dopa.
b- Psychological disturbances e.g. delusions, hallucinations aberrant sexual activity. Either reduce the dose of L-DOPA or use the atypical antipsychotic ***Clozapine***.

3- Eye: Mydriasis & may ↑ IOP.

4- C.V.S.: Tachycardia, arrhythmias, postural hypotension or Hypertension (LD or MAO-I).

5- G.I.T.: Nausea and vomiting that can be treated by ***Domperidone***.
Constipation and sometimes bleeding peptic ulcer.

6- Rarely *hemolytic anemia* with +ve Coombs' test.

* Contraindications:

1- Psychological disturbances.
2- Closed angle glaucoma.
3- Cardiac diseases.
4- Peptic ulcer
5- Malignant melanoma.
6- Unfavorable drug-Interactions.

2) COMT Inhibitors

L-DOPA $\xrightarrow{COMT}$ 3-0-Methyl-Dopa → Compete with L-Dopa for uptake by CNS.

a- **Tolcapone** → Hepatotoxic.
b- **Entacapone** → Less Toxic.

3- Selegiline (Deprenyl, Jumex):

1- In small dose < 10 mg → ***Selective MAO-B inhibitor***.
2- ***Potentiates*** effect of L-DOPA.
3- **Neuroprotective** effect → ↓ oxidative metabolites of dopamine & MPTP:
a- DA + O_2 + $H_2O \xrightarrow{MAO\text{-}B}$ DOPAC + NH_3 + H_2O_2 → H_2O_2 + Fe^{+2} → OH^- + OH^- + Fe^{+3}.
b- Methyl Phenyl Tetrahydro-Pyridine (MPTP) $\xrightarrow{MAO}$ Methyl Phenyl Pyridinium$^+$.
4- **Side Effects**:
a- Formation of Amphetamine & Methamphetamine → CNS Stimulation.
b- interaction with Meperidine → Hyperthermia, agitation & rigidity.

4- Direct Dopamine Agonists

A) Ergolines = Ergot Alkaloids:

1- Bromocriptine *(Parlodel)*:

1- **Direct** Dopamine D_2-Agonist & D_1-Partial agonist.
3- **Absorbed** orally. Longer plasma $t_{1/2}$ = 7 Hs.
4- **Advantages** over l-DOPA:
a- Does not need synthesizing enzymes & More specific on D_2 receptors.
b- No active transport system. No competition with aminoacids.
c- No toxic oxidative metabolites.
d- Longer $t_{1/2}$ → Less fluctuations in response.
3- **Used** in (7.5 - 30 mg orally):
a- Parkinsonism → Monotherapy or as Add-on to Sinemet.
b- ↓ Prolactin → Treat Hyperprolactinemia e.g. Galactorrhea-amenorrhea syndrome.
c- Suppress lactation. Safer than Estrogen.
d- Acromegaly.

4- **Side effects & Contraindications of Bromocriptine** :
   a- CNS: Dyskinesias and mental disturbances.
   b- GIT: Anorexia, nausea, vomiting, dyspepsia, constipation & bleeding peptic ulcer.
   c- CVS: Arrhythmia, hypotension (first dose) & digital vasospasm.
   d- Erythromyalgia (Erythromelalgia).

NB)

1- Other Ergolines: ***Lisuride & Pergolide*** (Permax 3 mg / day) → Direct D_1 + D_2- Agonist.
2- Non-Ergot Direct D-Agonists → ***Pramipexole*** & ***Ropinirole***.

5- Amantadine *(Symmetrel)* :

1- **Antiviral** agent in prophylaxis of influenza A_2.
2- Acts mainly by ↑ **Release** & ↓ **Uptake** of Dopamine.
3- **Less** efficacious than Sinemet. Its effect wears off within few weeks.
4- **Dose** = 100 mg bid orally.
5- **Side effects**:
   a- CNS disturbances up to acute toxic psychosis.
   b- CVS : Hypotension, CHF and peripheral edema
   b- GIT disturbances.

B) Anti-muscarinic Drugs:

1- Parasympatholytics:

A) *Natural Belladonna Alkaloids*: Atropine & Hyoscine
B) *Synthetic Atropine Substitutes*: If one fails try another

- **Benztropine** (Cogentin) 1 - 2 mg bid.
- **Trihexyphenidyl** = **Benzhexol** (Parkinol, Artane) 2 - 4 mg tds.
- **Biperiden** (Akineton) 2 - 12 mg/day.

1- Treat mainly tremors, rigidity & Salivation.
2- **Uses:**
   a- Add-on to L-DOPA.
   b- Used mainly to treat Iatrogenic Parkinsonism induced by neuroleptic drugs.
3- **Side effects & Contraindications** similar to atropine → Glaucoma & Senile BPH.

2- Anti-Histaminics with Anti-Cholinergic Activity e.g. Diphenhydramine.

3- Ethopropazine → Phenothiazine → Treat Oculo-gyric crisis.

NB) Iatrogenic Parkinsonism = Drugs Contra-indicated :

1- Block of Central D_2-receptors:
a- Neuroleptic drugs : Phenothiazines & Butyrophenones.
b- Antiemetics : Metoclopramide.
2- Depletion of Dopamine stores: Reserpine.
3- Inhibition of Dopamine synthesis: α-methyl dopa (Aldomet).
4- Destruction of Dopamine neurons: MPTP.
5- Cholinomimetics that pass BBB: Physostigmine & pilocarpine.

Treatment Of Epilepsy

* Types of epilepsy:

A) Partial = Focal Seizures: Epileptic focus → Local discharge

1- **Simple Partial *(Jacksonian Epilepsy)*:** NO loss of consciousness. Focus in Frontal lobe → Clonic jerking of single limb or a muscle group lasting for about 2 minutes. There may be some sensory disturbance.
2- **Complex Partial (Psycho-Motor & Psycho-Sensory) Seizures:** Focus in Temporal lobe → Attacks of Confused behavior with Purposeless movements & Sensory hallucinations. There is brief impairment of consciousness followed by amnesia of the attack.
3- **Partial with Secondarily Generalized Seizures:** Partial seizure that is followed immediately by generalized (grand mal) attack due to spread of the discharge.

B) Generalized Seizures: Abnormal Discharge affects both hemispheres.

1- **Tonic-clonic (Grand mal) Epilepsy:** Aura → Loss of consciousness → Tonic spasm (1 min.) → Clonic jerking → Flaccid relaxation → Confusion & Fatigue → Sleep.
2- **Absence (Petit mal) Epilepsy:** Brief sudden attack of loss of consciousness lasting only for 10-15 seconds with mild or no motor disturbances. Begins in childhood (2-12 years), may stop at age of 20 or change to Grand mal epilepsy.
3- **Myoclonic seizures:** Short jerking of the whole body or one of the extremities withOUT loss of consciousness.
4- **Atonic seizures:** Sudden loss of postural tone → Fall.

C) Status Epilepticus: Severe sustained seizures without period or recovery. It occurs in ALL types of epilepsy especially if treatment is irregular or suddenly stopped. An Emergency → Permanent brain damage or FATAL.

* Specific Anti-Epileptic Drugs:

A) Aim of Therapy:

1- Selective inhibition of the Epileptogenic focus.
2- Prevent spread of the abnormal impulses in the surrounding normal brain tissue.
3- Treatment should be continued for 2-3 years fit-free.
4- Withdraw Anti-Epileptic drugs gradually to avoid Status Epilepticus.

B) Mechanism of Action of Anti-Epileptic Drugs:

1- **Block of Na^+-channels** → Delay recovery → Treat Partial & Grand Mal e.g. Phenytoin, Carbamazepine, Lmotrigine & Valproate.
2- **Block of voltage dependent T-Calcium channels** → Treat Petit Mal e.g. Ethosuximide, Trimethadione & Valproate.
3- **Enhance GHABA-Transmission**:
   a- GABA-Potentiators e.g. Barbiturates & Benzodiazepines.
   b- ↓ GABA metabolism e.g. Vigabatrin & Valproate.
4- **Block excitatory transmitters** (Glutamate & Aspartate) e.g. Felbamate.

ANTI-EPILEPTIC DRUGS

I - Barbiturates:

1- ***Phenobarbital*** : Effective in sub-hypnotic dose (100-300 mg/Day).

2- ***Mephobarbital*** : 75% is converted to Phenobarbital in liver.

3- ***Primidone*** *(Mysoline, 500 – 1500 mg / day)* Active → 2 Active Metabolites →
a- 20% Phenobarbitone and
b- 80% Phenyl-ethyl-malon-amide (PEMA).

* *Mechanism Anti-Epileptic Effects*:

1- Facilitate $GABA_A$ transmission → Cl^- influx → Hyperpolarization → Postsynaptic inhibition.
2- ↓ Ca^{2+} influx by presynaptic nerve endings → ↓ Release of excitatory mediators.

* *Use in Epilepsy*:

1- Partial & Grand Mal → NOT drug of choice → Sedation, Tolerance & Dependence.
2- Phenobarbitone 10 – 20 mg / kg Slow I.V. → Status Epilepticus
3- Worsen Petit Mal Epilepsy.

* *Adverse Effects*:

1- Tolerance & Dependence.
2- S E D A T I O N.
3- Behavioral changes → Irritability, hyperactivity, confusion & agitation.
4- Cerebello-Vestibular disturbances → Ataxia, Nystagmus & Vertigo.
5- Hepatic Microsomal Enzyme Induction:
   a- ↑ Their own metabolism → Tolerance & Failure of Anti-Epileptic activity.
   b- ↑ Metabolism of Other Anti-Epileptic drugs e.g. Phenytoin & Carbamazepine.
   c- ↑ Metabolism of other drugs e.g. Oral contraceptives.
   d- ↑ Metabolism of Folic Acid → Megaloplastic anemia.
   e- ↑ Metabolism of Vit D → Hypocalcemia → Osteomalacia.
   f- ↑ Metabolism of Vit K → Hypoprothrombinemia.
6- Other adverse effects e.g. Acute Porphyria (see Sedatives & Hypnotics).

2- *Hydantoin Derivatives*

1- Phenytoin (Diphenyl-Hydantoin, Epanutin)

* Kinetics:

1- **Absorption**:
   a- Oral: - Irritant (Used after meals) & affected by particle shape & size (Polymorphism).
   b- I.M. → Irregular absorption.
   c- Slow I.V. in Status epilepticus.
2- **Distribution** All-over the body. Highly bound to plasma albumin (80-90%)
3- **Metabolized** by Hepatic Microsomal Enzymes → Hydroxylation then conjugation with glucuronic acid:
   a- *Small dose* → First-Order Kinetics → Constant t ½
   b- *Large dose* → Zero-Order Kinetics → ↑ t ½ with ↑ Dose.

* Actions & Uses of Phenytoin:

1- **Block Na^+-channel** → Delay recovery → ↓ Rate of firing → Membrane stabilization.
2- **Anti-Epileptic**:
   a- *Drug of Choice* (No Sedation) in *Partial seizures & Grand Mal* Epilepsy (200–400 mg/ day, Optimum plasma concentration = 10 – 20 ug / ml). Monitor plasma level.
   b- *Status Epilepticus* (15 – 20 mg / kg body weight Slow I.V.).
   c- *Worsens* Petit Mal epilepsy.
3- **Class-1 Group-B Anti-Arrhythmic** → Useful in treatment of Ventricular arrhythmia with Heart Block → Drug of Choice in *Digitalis-Induced arrhythmia*.
4- Treatment of **Trigeminal neuralgia**.

* Adverse Effects of Phenytoin:

1- Confused behavior → Confusion & Hallucinations.
2- Gum (Gingival) Hyperplasia especially in Children → Irreversible → Consult Dentists.
3- Gastric irritation (highly alkaline) → Used after meals.
4- Hirsutism (Androgenic effect).
5- Hepatotoxicity.
6- Hypersensitivity → Lymphadenopathy (Misdiagnosed for Hodjkin's disease) & Lupus.
7- Hormones → ↓ Release of A.D.H. & Insulin → Hyperglycemia.
8- Ataxia, Nystagmus & Vertigo → Cerebello-Vestibular manifestations.
9- Agranulocytosis.
10- During Pregnancy:
   a- First trimester → Teratogenic → Fetal Hydantoin Syndrome → Hare lip & Cleft palate
   b- Before labor → Hypoprothrombinemia in baby → Bleeding → Prevented & treated by Vit-K.
11- Drug Interactions:
   a- Phenytoin → Hepatic Microsomal Enzyme Inducer:
      - ↑ Its own metabolism → Tolerance & Failure of Anti-Epileptic activity.
      - ↑ Metabolism of Other Anti-Epileptic drugs e.g. Barbiturates & Carbamazepine.
      - ↑ Metabolism of other drugs e.g. Oral contraceptives.
      - ↑ Metabolism of Folic Acid & ↓ Its intestinal absorption → Megaloplastic anemia & ↑ Toxicity of Methotrexate (Folate antagonist).
      - ↑ Metabolism of Vit D → Hypocalcemia → Osteomalacia.
      - ↑ Metabolism of Vit K → Hypoprothrombinemia.
   b- HME Inducers e.g. Phenobarbitone & Carbamazepine → ↑ Metabolism of Phenytoin.
   c- HME Inhibitors e.g. Valproate, Cimetidine & Isoniazide → ↓ Metabolism of Phenytoin.
   d- Phenytoin displaces Thyroxin & Tricyclic Anti-Depressants from plasma proteins.
   e- Aspirin, Sulfa & Valproate → Displace phenytoin from plasma proteins.

NB) Other Hydantoin Derivatives:

1- **Mephenytoin** → More toxic than Phenytoin.
2- **Ethotoin** → Less toxic *but* less effective than Phenytoin.

3- Carbamazepine *(Tegretol) 600 – 1200 mg / day*

1- Carbamazepine → Active epoxide metabolite.
2- Related to Tri-cyclic **Anti**-depressants → Useful as Mood Stabilizer in patients with Manic-Depressive (Bipolar affective) Disorders.
3- **Anti**-Epileptic → Similar to Phenytoin → Blocks Na^+-channels → Drug of Choice (NO Sedation) in Partial & Grand Mal Epilepsy (Optimum plasma level = 6 - 12 ug/ml) Worsens Petit Mal Epilepsy.
4- **Anti** -Diuretic → Treats Hypothalamo-pituitary Diabetes mellitus.
5- Treats **Tri**geminal neuralgia.
6- Hepatic Microsomal Enzyme Inducer (see Phenytoin)
7- Adverse Effects:
   a- Allergy
   b- Ataxia, Nystagmus & Vertigo → Cerebello-Vestibular
   c- Anorexia → G.I.T. upset
   d- Anti-diuretic → Fluid retention
   e- Hepatitis
   f- Teratogenic → Similar to Fetal Hydantoin Syndrome.
   g- Bone marrow inhibition

NB) Oxcarbazepine (Trileptal) 600 – 1200 mg / day

1- Related to carbamazepine *But* less toxic & Less HME induction
2- Oxcarbazepine → Active hydroxyl-metabolite

NB) Barbiturates, Phenytoin & Carbamazepine:

1- Treat Partial & Grand Mal Epilepsy.
2- Worsens Petit Mal Epilepsy.
3- H.M.E. Inducers.

ℂ ℂ ℂ ℂ ℂ ℂ ℂ ℂ ℂ ℂ ℂ ℂ ℂ ℂ ℂ

4- Succinamide Derivatives

1- Ethosuximide *(Zarontin)*:

1- **Anti-Epileptic**:
   a- Block Voltage dependent **T-Calcium channels**.
   b- Drug of **Choice in Absence Seizures** = Petit Mal Epilepsy & *Psychomotor* epilepsy (0.5-1.5 g / day, Optimum plasma level 40-100 ug/ml).
   c- *Worsens* Grand Mal Epilepsy.
2- **Adverse Effects**:
   a- C.N.S. → Drowsiness, Lethargy & Behavioral changes.
   b- G.I.T. upset. C- Allergy → Lupus & Blood dyscrasias.
3- **Other Succinamides** → *Methsuximide* & *Phensuximide* → Not Drug Of Choice

5- Oxazolidinedione Derivatives

1- Examples:
   a- *Trimethadione* → Dimethadione (Active metabolite).
   b- *Paramethadione*
2- Block Voltage dependent T-Ca^{2+} channels → Treat Petit Mal epilepsy (Not drug of Choice) & Worsens Grand Mal epilepsy.
3- Adverse Effects:
   a- **Hemeralopia** = Glare effect → Intolerance to light → Wear Dark glasses
   b- Allergy c- CNS → Sedation d- GIT upset
   e- Hepatotoxicity f- Nephrotoxicity g- Bone marrow depression

6- Acetazolamide (Diamox)

1- *Carbonic anhydrase inhibitor* → ↑ CO_2 & Acidosis → ↓ C.N.S. excitability → Useful in Resistant Absence seizures (Petit mal epilepsy) & Not *Grand mal epilepsy.*
2- *Many side effects* e.g. Hypokalemia, acidosis, alkaline urine & sedation (See Diuretics).

NB) Ethosuximide, Trimethadione & Acetazolamide → Useful in Petit mal epilepsy & *Not* in Grand mal epilepsy.

7- Valproic Acid & Sodium Valproate *(Depakene, Epilim) 1-3 g*

** Anti-Epileptic Effect:*

1- **Mechanism of Action**:
   a- Block Na^{+}-channels → Similar to Phenytoin → Effective in Partial & Grand Mal epilepsy.
   b- Block T-Ca^{2+}-Channels → Similar to Ethosuximide → Effective in Absence seizures.
   c- ↓ GABA-transaminase enzyme → ↑ GABA.
   d- Antagonise excitatory transmitters e.g. Aspartate.

2- **Therapeutic use** → 1-3 g / day, Optimum plasma level 30 – 100 ug / ml.
   a- Broad spectrum Anti-epileptic useful in Partial seizures, Grand mal & Petit mal epilepsy (Not drug of choice → Sedation & Hepatotoxic).
   b- Drug of choice in patients with:
      - Mixed Petit mal + Grand mal epilepsy.
      - Myoclonic epilepsy.

3- **Other Uses**:
   a- Anti-manic & Mood stabilizer in Bipolar Affective disorders.
   b- Migraine headache.

3- **Adverse Effects**:
   a- Allergy b- Temporary loss of hair → Thin curly hair.
   c- C.N.S. → Sedation d- G.I.T. → Nausea & Vomiting.
   e- Hepatotoxicity.
   f- Hematological → Thrombocytopenia & ↓ Platelet aggregation → Hemorrahge.
   g- Teratogenic → Spina bifida.
   h- Drug Interaction:
      - Enzyme inhibitors → ↓ Metabolism of Phenytoin, carbamazepine & barbiturates.
      - Displaces phenytoin from plasma proteins.

8- Benzodiazepines

1- **Mechanism of Action** → ↑ GABA-A transmission → ↑ Cl^- influx → Hyperpolarization → Post-synaptic inhibition.

2- **Diazepam** 10 mg SLOW I.V. → Drug of Choice in Status epilepticus.

3- **Clonazepam**:

a- Slow I.V. 1 mg → treat Status epilepticus.

b- Orally 4 mg → Broad spectrum anti-epileptic in Partial, Grand mal, Petit mal & Myoclonic epilepsy → Not drug of choice.

c- *Adverse Effects*:

- Tolerance - Dependence - Sedation & Behavioral changes
- ↑ Secretions → Salivary & Bronchial

9- New Anti-Epileptic Drugs

May be used as Monotherapy or as Add-on in resistant cases of Eilepsy.

1- Lamotrigine (Lamictal): 50 – 200 mg / day

a- Block Na^+-channel & Antagonizes excitatory transmitters e.g. Glutamate & Aspartate.

b- Adverse effects → Skin rash & Dermatitis.

2- Topiramate *(Topamax)*: 200 – 1000 mg / day

a- Block Na^+-channel & Antagonize excitatory transmitters e.g. Glutamate & Aspartate.

b- Adverse effects → Sedation & confusion.

3- Felbamate:

a- Antagonize excitatory transmitters e.g. Glutamate & Aspartate

b- May produce *fatal* aplastic anemia.

4- Vigabatrin *(sabril) 1000 mg / day*

a- Irreversible ↓ of GABA-Transaminase → ↑ GABA

b- Produces psychiatric disturbances → Depression & psychosis

5- Gabapentin *(Neurontin) 1200 mg / day*

a- ↑ Release of GABA. b- Side effects → Sedation & Ataxia

6- Tiagabin → ↓ GABA uptake.

* Choice of Anti-Epileptic Drugs:

A) Generalized Tonic-Clonic Seizures = Grand Mal Epilepsy:

1- First Choice: Carbamazepine & Phenytoin.

2- Alternative: Valproate

3- Phenobarbital & Primidone

B) Partial Seizures:

1- First Choice: Carbamazepine & Phenytoin.

2- Alternative:

a- Valproate. b- Lamotrigine, Vigabatrin & Gabapentin → Monotherapy or Add-on.

3- Phenobarbital & Primidone.

C) Absence Seizures = Petit Mal Epilepsy:

1- First Choice: Ethosuximide
2- Alternative:
   a- Valproate. b- Lamotrigine as Add-on c- Clonazepam.
3- Trimethadione & Paramethadione.
4- Acetazolamide

D) Mixed Petit mal + Grand mal epilepsy } - Drug of Choice → Valproate.
E) Myoclonic Seizures } - Alternative → Clonazepam

F) Status Epilepticus:

1- Diazepam 10 mg Slow I.V.
2- Clonazepam 1 mg Slow I.V.
3- Phenytoin 15-20 mg / kg Slow I.V.
4- Phenobarbitone 10 – 20 mg / kg Slow I.V.
5- Paraldehyde 4 – 8 ml I.M.

	Mechanism	H.M.E.	Grand Mal	Partial	Petit Mal	Status Epilepticus
1- Phenobarbital	↑ GABA-A transmission	↑	+	+	#	+
2- Phenytoin	Block Na^+	↑	Choice	Choice	#	+
3- Carbamazepine	Block Na^+	↑	Choice	Choice	#	
4- Ethosuximide	Block Ca^{2+}		#	+	Choice	
5- Trimethadione	Block Ca^{2+}		#	+	+	
6- Acetazolamide	↓ Carbonic anhydrase		#		+	
7- Valproate	↓ Na^+, ↓ Ca^{2+} & ↑ GABA	↓	+	+	+	
8- Diazepam	↑ GABA-A transmission					Choice
9- Clonazepam	↑ GABA-A transmission		+	+	+	Choice
10- Lamotrigine	↓ Na^+		+	+	+	
11- Vigabatrin	↓ GABA-transaminase		+	+	+	
12- Gabapentin	↑ GABA release		+	+	+	

NB) Anti-Epileptics & Hepatic Microsomal Enzymes:

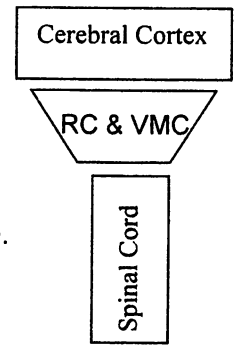
1- **HME Inducers** → Barbiturates, Phenytoin & Carbamazepine.
2- **HME Inhibitor** → Valproates.

NB) Anti-Epileptics & Pregnancy:

1- **Early pregnancy (First Trimester)** → Teratogenic.
   Teratogenicity is reduced by intake of folic acid during pregnancy.
   a- *Phenytoin & Carbamazepine* → Fetal phenytoin Syndrome → Hare lip & Cleft palate
   b- *Valproates* → Spina bifida.
2- **Before labor** → Anti-epileptic enzyme inducers e.g. Barbiturates, Phenytoin & Carbamazepine → ↑ Vit K metabolism → Hypoprothrombinemia → ↑ Bleeding in neonates. Prevented by Vit K to mother before labor.

C.N.S. Stimulants

1- Cerebral Cortex Stimulants:



a- Methyl-xanthines e.g. Caffeine.
b- Methylphenidate *(Ritaline)*:
Similar to Amphetamine *BUT* Weaker & Less toxic.
c- Cocaine (see Local Anesthetics).
d- Autonomic drugs e.g. Ephedrine, Amphetamine & Atropine.

2- Brain Stem Stimulants → Analeptics.

3- Spinal Cord Stimulants → Strychnine.

Strychnine

Alkaloid of Strychnos Nux-vomica seeds (الجـوز المقـيئ)

* Pharmacodynamics:

1- C.N.S. Stimulation in an Ascending order:

Anti-Glycine → ↑ Polysynaptic pathways mainly in spinal cord.
a- ↑ Polysynaptic spinal reflexes e.g. withdrawal reflex.
b- ↑ Medullary R.C. & V.M.C. → Analeptic.
c- ↑ Cortex → ↑ Sensations.

2- G.I.T.: Bitter taste → Stomachic.

* Toxicity → Tonic = Tetanic Convulsions

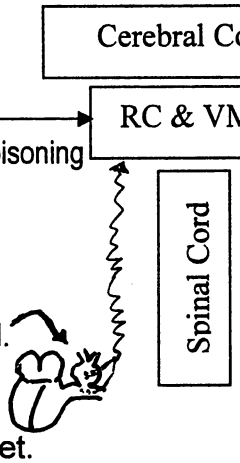
1- Origin → Spinal cord.
2- Characters → Reflex (to external stimulus), Symmetrical & Non-coordinated.
3- Cause of Death → Spasm of respiratory muscles.
4- Treatment → ***Mephenesine***.
a- Dark quite circumstances.
b- Anesthesia either inhalation or I.V. Thiopentone or Diazepam.
c- Specific Antidote → ***Mephenesine***.
d- Stomach wash if it is taken orally:
- Tannic acid (Strong tea) → Precipitate Strychnine
- K permanganate or Tincture Iodine → Oxidize Strychnine.

Analeptics

C.N.S. stimulants characterized by:

1- ↑ Vital Medullary Centers (R.C. & V.M.C.) specially when they depressed. Minimal effect on normal centers.
2- Can *Awaken* deeply anesthetized patients.
3- Toxic dose → ***Clonic convulsions***:
   a- ***Clonic convulsions***:
      - Origin → Supra-spinal e.g. Midbrain.
      - Characters → Spontaneous, Asymmetrical & Coordinated.
      - Cause of death → Exhaustion of respiration (Center & muscles).
      - Antidote → I.V. Barbiturates.
   b- Sometimes Clonic convulsions may be followed by ***Tonic*** convulsions due to descending stimulation of spinal cord.
   c- Treatment of Toxicity → I.V. Barbiturates ± Mephenesine.

	Tonic (Tetanic) Convulsion	Clonic Convulsions
1- Cause:	Strychnine	Analeptics
2- Origin:	Spinal cord	Supra-spinal
3- Characters:	Reflex Symmetrical Non-coordinated	Spontaneous Asymmetrical Coordinated
4- Cause of Death:	Spasm of respiratory muscles	Exhaustion of Respiration
5- Treatment:	Mephenesine & Barbiturates	Barbiturates



A) Direct Analeptics:
1- Megemide → Treat Bb poisoning
2- Cardiazole
3- Picrotoxine: Anti-GABA

B) Indirect Analeptics:
- Lobeline I.U. in neonatal.

C) Dual Analeptics:
1- Nikethamide → Liver met.
2- Ethamivan: I.U. in Neonat
3- Amiphenazole
4- Doxapram → Safest
5- Carbogen: 5% CO_2 + O_2.

D) Reflex Analeptics:
1- Ammonia inhalation.
2- Alcohol ingestion.
3- Camphor S.C. injection.

E) Specific Anatgonists:
1- Naloxone in Morphine poisoning
2- Flumazenil in Bz poisoning.

F) Other C.N.S. Stimulants:
1- Cortex: Caffeine .
2- Spinal cord: Strychnine.

* *Classification Of Analeptics:*

They are classified according to their *mechanism* of action:

A) Direct: Direct ↑ of R.C. & V.M.C. specially when they are depressed

1- Megemide (Bemegride):

a- Quick onset *BUT* short duration.

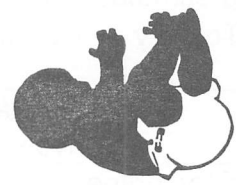
b- Useful (50 mg I.V.) in Barbiturate poisoning (Not specific antidote).

2- Pentylenetetrazole (P.T.Z., Cardiazole, Leptazole):

a- General C.N.S. stimulant.

b- Uses:

- Analeptic *BUT* narrow safety margin → Convulsions.
- Diagnosis of Epilepsy → E.E.G. changes.
- Convulsive therapy in psychiatry.



3- Picrotoxine:

a- Plant alkaloid → Anti-GABA

b- Narrow safety margin → Convulsions.

B) Indirect: →

1- They ↑ Chemoreceptors in aortic & carotid bodies → Reflex stimulation of R.C. & V.M.C

2- Example: **Lobeline** *was* used Intra-umbilical in neonatal asphyxia.
Cross tolerance with nicotine.

C) Dual:

BOTH Direct (↑ Sensitivity to CO_2) & Indirect (Chemoreceptors) ↑ of Vital centers.

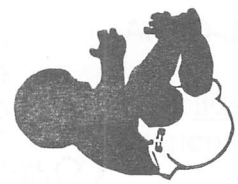
1- Nikethamide (Coramine):

Extensive hepatic metabolism → Nicotinamide (member of Vit-B) → Low oral bioavailability. Oral dose > I.M. & I.V. doses.

2- Ethamivan (Emivan):

a- Related chemically to Nikethamide.

b- Useful I.U. in neonatal asphyxia.



3- Amiphenazole (Daptazole).

4- Doxapram (Dopram):

a- The ***SAFEST*** analeptic → Used I.V. infusion to accelerate recovery from anesthesia.

b- Large dose → Hypertension, nausea & convulsions.

5- Carbogen: 5% CO_2 + O_2 inhalation

Methyl-Xanthines

1- They include → **Caffeine, Theophylline (Aminophylline) & Theobromine.**
2- Natural Alkaloids of plant origin.
3- They are present naturally in caffeinated beverages:
   a- Tea leaves: Caffeine (30 -50 mg) + Theophylline..
   b- Coffee seeds: Caffeine (100 – 150 mg).
   c- Cola: Caffeine (30 – 50mg).
   d- Cocoa: Caffeine (5 – 8 mg) + Theobromine

* Pharmacokinetics:

1- Absorbed orally, rectally (suppository) & parenterally.
2- Distributed allover the body. They pass B.B.B. & placental barriers.
3- Metabolism → **ethyluric acid** → Soluble → **NOT** contraindicated in gout.

* Pharmacodynamics:

A) Mechanism of Action:

Sympathomimetics β-Agonists (+ +) → A.T.P. —Adenylate cyclase→ Active 3' 5' cAMP —Phosphodiesterase→ Inactive 5 AMP ← (- -) *Methylxanthines*

1- Inhibit Phosphodiesterase enzyme IV (PDE-4) → ↑ cAMP.
2- Block adenosine receptors in C.N.S. & periphery.
3- ↑ Sympathetic: ↑ Release of catecholamines & COMT-Inhibitor.

B) Pharmacological Actions:

Caffeine is Stronger on → CNS, Sk.m. & Gastric acidity (المخ و العضلات و المعدة)
Theophylline (Aminophylline) is Stronger → Other actins

1- C.N.S. Stimulation in a descending manner (Specially Caffeine):
a- ↑ Cortex → Mental activity, alertness, ↑ Acuity of sensations & Anti-fatigue.
   Large dose → Insomnia, anxiety & tremors specially in children.
b- ↑ Medulla: ↑ R.C. (Analeptic), ↑ V.M.C., ↑ Vagal center (C.I.C.).
c- ↑ Spinal cord.

2- C.V.S.: (Specially Theophylline)

a- Heart → Direct (↑cAMP) → ↑ Heart → [↑ H.R.], ↑ Contractility, ↑ Work & ↑ Automaticity
   Heart → C.N.S. → ↑ C.I.C. → [↓ H.R.]
b- B.V. → Direct (↑ CAMP) → [V.D.] → ↓ Bl.p.
   B.V. → CNS → ↑ VMC → [V.C.] → ↑ Bl.p.

c- Aminophylline Small Dose & Slow I.V. → Minimal change in H.R. & Bl.p.
   While Large dose or rapid I.V. → Direct effect → Tachycardia + Hypotension
d- Cerebral V.C.

3- Respiration:

a- Direct (↑ cAMP) → Bronchodilatation specially Theophylline.
b- C.N.S. → ↑ R.C. specially Caffeine.

4- G.I.T.:

a- *Caffeine* → ↑ Gastric acidity, S.D. (↑ Motility) while L.D. (↓ Motility).
b- Theophylline → Spasmolytic & Irritant → Nausea & Vomiting.

5- Renal:

a- Theophylline → Spasmolytic on ureter & bladder.
b- Diuretic: (Theophylline > Theobromine (Longer) > Caffeine)
- Extra-Renal → ↑ C.O.P. + Renal V.D. → ↑ R.B.F. → ↑ G.F.R.
- Renal → ↓ Na & H_2O reabsorption from the nephrone.

6- Smooth Muscles → Spasmolytic specially Theophylline.

7- Skeletal Muscles → Stimulation & Anti-fatigue specially *Caffeine*.

* Therapeutic Uses Of Methyl-Xanthies:

A) Aminophylline (Theophylline Ethylene Diamine): 250 - 500 mg

(A , B , C , D)

1- ***A***nti-Spasmodic in colics.

2- ***B***ronchial Asthma:

a- *Mechanism of action*:
- ↑ PDE-4 → ↑ cAMP & Block adenosine receptors.
- Bronchodilatation, stabilization of Mast cells.
- Improve contraction of respiratory muscles e.g. Diaphragm.

b- *Indications*:
- *Acute attacks*: Aminophylline 250-500 mg Slow I.V. ± β_2-Agonists.
- *Status Asthmaticus*: I.V. infusion + Cortisol.
- *Prophylaxis:*
  # Theophylline S.R. 200 mg / 12 hours.
  # Aminophylline orally → Irritant → Gastritis.
  # Aminophylline suppository → Irritant → Proctitis specially in children.
  # *Choline theophyllinate* orally → Less irritant.

  # ***Enprofylline*** → Similar to theophylline *BUT*:
  i- More potent ii- Less toxic iii- NOT metabolized → Longer
  iv- NOT block Adenosine receptors v- NOT diuretic

3- Chronic Obstructive Pulmonary Diseases (COPD) e.g. Emphysema.
4- Apnea in neonates.

5- **C**ardiac Asthma = Left Ventricular failure = Pulmonary edema:
Aminophylline I.V. or suppository:
a- +ve Inotropic *BUT* short duration = 30 min (Add Digoxin).
b- Diuretic c- Bronchodilator

6- **D**iuretic → Used to potentiate other diuretics.

B) Caffeine: 100 - 300 mg Orally & I.M. (E , F , G , H)

7- With **E**rgotamine → Cafergot in Migraine headache.
With Aspirin in simple headache.
8- **F**atigue (Physical or mental).
9- With Neostigmine in Myasthenia **G**ravis.
10- Poisoning by C.N.S. depressants e.g. **H**ypnotics.

C) Pentoxyfylline *(Trental)*: (I)

11- Chronic occlusive arterial diseases e.g. **I**ntermittent claudication:
a- Improves RBCs flexibility & ↓ Plasma fibrinogen → ↓ Blood viscosity
b- ↓ Platelet aggregation.

* Adverse Effects Of Xanthines:

A) Caffeine: *(Wide safety margin)*

1- C.N.S. → Insomnia, anxiety & tremors.
2- G.I.T. → Hyperacidity.

B) Theophylline (Aminophylline):

1- **Narrow range** of therapeutic plasma concentration → 10 – 20 ug /ml.

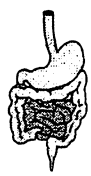
2- **Irritant**:
a- I.M. or S.C. → Painful.
b- Orally → Gastritis (use after meals)
c- Rectally (suppository) → Proctitis specially in children.

3- **Rapid I.V. injection** → Velocity reaction:
a- Heart: - Theophylline → Tachycardia & Arrhythmia
- Ethylene diamine → Cardiac arrest.
b- Bl.p. → Severe hypotension & syncope.
} May be FATAL

4- **C.N.S.**: Insomnia, anxiety, tremors & seizures specially in children.

5- **C.V.S.**: Tachycardia, palpitation, angina, arrhythmia & hypotension.

6- **G.I.T.**: Anorexia, nausea, vomiting & ulceration.



C) Long Use:

1- **Tolerance** & Cross tolerance between the xanthines.
2- Psychic dependence = **Habituation**.

* Contraindications of Xanthines:

1- Angina (↑ cardiac work), Arrhythmia (↑Automaticity) & Hypertension (Caffeine)
2- Peptic ulcer → Not used orally.
3- Tea → Tannic acid → Precipitates:
   a- GIT surface proteins = *Astringent* → Constipation.
   b- Iron → Hypochromic microcytic anemia.

* Drug Interactions of Theophylline:

A) Drugs ↓ Metabolism of Theophylline → ↑ Its plasma level → Toxicity

a- Cimetidine.
b- Antimicrobials: Erythromycin & Quinolones.
c- Heart & Hepatic Diseases, and Hypothyroidism.

B) Drugs↑ Metabolism of Theophylline → ↓ Its Plasma level → ↓ Effect

a- Rifampicine.
b- Anti-Epileptics: Phenobarbitone, Phenytoin & Carabamazepine.
c- Hyperthyroidism
d- Tobacco (Heavy smokers) & Alcohol.

Anesthesia

General Anesthesia

- A state of *Reversible* C.N.S. inhibition characterized by *Loss* of *Consciousness*, *Sensations* & *Motor activity* to an extent allowing the performance of easy & painless operation.
- General anesthetics depress the C.N.S. in a *descending manner*. They act primarily on the *Reticular formation*. Vital medullary centers are the last to be depressed.

* Stages of General Anesthesia:

A) First Stage (Induction , Analgesia): ↓ Sensory Cortical area

***1- Begins*:** Administration of the anesthetic.
***2- Ends*:** Loss of consciousness.
***3- Characteristics*:**
a- Patient is conscious.
b- ↑ Hearing acuity.
c- Analgesia.

B) Second Stage (Excitement , Delirium): ↓ R.F.

***1- Begins*:** Loss of consciousness *Then* Excitation.
***2- Ends*:** Normalization of Respiration & Circulation.
***3- Characteristics*:**
a- Release of subconscious emotions.
b- Increased involuntary motor activity.
c- Respiration is irregular.
d- Tachycardia & Hypertension. } Stress → ↑ Sympathetic → ↑ Catecholamines
e- Active mydriasis.
f- Reflexes are intact e.g. swallowing.
g- Vomiting may occur.

C) Third Stage (Surgical Anesthesia): ↓ Spinal cord from below upwards

***1- Begins*:**
a- Patient is quite.
b- Respiration is regular & equally abdominal and thoracic.
c- Normal heart rate & blood pressure.
d- Normal size of pupil. Eyes are roving.
e- Loss of eye lid & conjunctival reflexes.
f- No swallowing or vomiting.
***2- Ends*:** Stop of respiration.
Management → Stop anesthesia + Administer Carbogen (5% CO_2 + O_2)
***3- Characteristics*:** Divided into 4 *Planes* according to Respiration & the Eye.

	Plane 1	Plane 2	Plane 3	Plane 4
1- Respiration:				
a- Thoracic (Intercostal)	Normal	Shallow & Lagging	Stop	Stop
b- Diaphragm (Abdominal)	Normal	Normal	Shallow	Stop
2- Eye:				
a- Movement	Roving	Fixed	Fixed	Fixed
b- Pupil size	Normal	PPP → Normal → Mydriasis	Mydriasis	Mydriasis
c- Lost reflexes	Eye lid & Conjunctival	Corneal	Light	All

D) Fourth Stage (Medullary Paralysis): ↓ Vital Medullary Centers

1- ***Begins***: Stop of respiration.
2- ***Ends***: Circulatory failure → Death
3- ***Characteristics***:
- a- Respiration → Stop.
- b- Eyes →Fixed lusterless with Dilated Non-reactive pupils.
- c- Hypotension & very weak pulse.
- d- Absent All reflexes.

4- ***Resuscitation***:
- a- Stop anesthetic.
- b- Artificial respiration.
- c- Analeptics e.g. *Doxapram* I.V. infusion.
- d- All anesthetics stop respiration before circulation → Resuscitation is possible *Except Chloroform* → Stop circulation with or before respiration → Obsolete.

Classification of General Anesthetics

I- Inhalation Anesthetics:

A) Volatile Liquid Anesthetics:

1- Ethers: Diethyl Ether & Divinyl Ether.

2- Halogenated Anesthetics:

NB) Most of them:
*1- **Cardiotoxic**:*
a- 1st Stage → ↑ Vagal tone → Bradycardia & Heart block # Atropine.
b- 2nd Stage → Sensitize myocardium to catecholamines → Arrhythmia # Propranolol.
c- 3rd Stage → Direct myocardial depressant.
d- 4th Stage → Chloroform ↓ Circulation before Respiration → Failure of Resuscitation.
*2- **Hepatotoxic** : Avoid by Low fat & High CHO diet, Vit B_{12} & Methionine.*

1- Halothane (Fluothane) 2- Isoflourane 3- Enflurane 4- Fluroxene
5- Methoxyflurane 6- Desflurane 7- Sevoflurane
8- Trichloroethylene 9- Chloroform 10- Ethyl chloride

B) Anesthetic Gases: 1- **Nitrous Oxide** (N_2O). 2- Cyclopropane.

II- Intravenous Anesthetics:

1- Ultrashort Acting Barbiturates: Thiopentone, Hexobarbitone & Methohexitone.
2- Benzodiazepines: Diazepam, Lorazepam & Midazolam.
3- Ketamine: Dissociative anesthesia.
4- Neurolept Analgesia: Droperidol + Fentanyl = Thalamonal.
5- Propofol: 6- Propanidid 7- Etomidate 8- Althesin
9- Opioid Analgesics: IV Morphine (1-3 mg/lg) & Fentanyl (50-100 ug/hg).

III- Basal Anesthesia:

1- Thiopentone Rectally. 2- Diazepam IV. 3- Paraldehyde Rectally.

Inhalation Anesthetics

* Methods of Administration:

1- Open Method: Dropping of the anesthetic over a gauze mask.
2- Semi-open method: Similar to open method but use of many layers of gauze.
3- Anesthetic Machine → Flow-meter + Endotrachial tube
   a- Semi-closed method: Use of re-breathing bag and an expiratory valve.
   b- Closed method: Use of soda lime.
      Trichloroethylene + Soda lime → Dichloroacetylene → spontaneous explosive & neurotoxic to cranial nerves especially trigeminal.

* Distribution of Volatile Anesthetics:

1- Alveolar air → ***Absorbed*** → Pulmonary veins → Heart → Arteries → Tissues specially brain → Veins → Heart → Pulmonary artery → Alveolar air → ***Excretion***.
3- The ***Brain*** acquires largest concentration of anesthetic (Rich in lipid & blood supply).
4- ***Concentration*** of Anesthetic:
   - During induction: Arteries > Veins.
   - During anesthetic equilibrium: Artery = Vein.
   - During Recovery: Vein > Artery.
5- ***Fate***:
   a- Some anesthetics are *Not* metabolized → Excreted unchanged in Lung.
   b- Some anesthetics e.g. Halothane are partially metabolized in liver.

N.B.)

*1- **Depth of Anesthesia** → Depends on partial pressure (concentration) of anesthesia in brain.*

2- ***Rate of Induction & Recovery*** → Depend on the rapidity with which this partial pressure is reached or lost.

3- ***Factors Affecting Depth & Rate of Anesthesia***:

a- Anesthetic *Concentration in inspired air* (Alveoli): Higher → Faster induction.

b- *Pulmonary Ventilation*: Higher → Faster induction & Recovery.

c- *Pulmonary blood flow*: Higher → Faster induction & Recovery.

b- *Solubility of Anesthetic in Blood (Blood/Gas Partition Coefficient)*:

- Anesthetics highly soluble in blood (High partition Coefficient) e.g. Ether → Slow rates of induction & recovery.
- Anesthetics with low solubility in blood (Low partition coefficient) e.g. Nitrous oxide → Rapid rates of induction & recovery.

3- ***Minimum Alveolar Concentration (MAC)*** **:**

a- Minimal alveolar concentration of anesthetic → Anesthesia in 50% of patients.

b- The lower MAC = The more potent anesthetic.

1- Halothane (Flouthane)

Colorless volatile liquid of pleasant odor.

* Advantages:

1- Non-Inflammable, Non-Explosive. Boiling point 50°C.
2- Very potent (MAC = 0.75%).
3- Blood / Gas P.C. (2.3) → Rapid smooth induction and recovery
4- Non-irritant to respiratory tract. It produces Bronchodilatation.
5- Controlled Hypotension → Blood less area → Useful in plastic & neurosurgery.
   a- ↓ VMC. b- Ganglion blocker. c- α-Blocker.
   d- Direct VD. e- Direct cardiac depressant.
6- Does not react with soda lime → Better than Trichloroethylene.
7- Little diffusion hypoxia → Better than Nitrous oxide.
8- Little post-anesthetic vomiting.

* Disadvantages:

1- Expensive.
2- Stages are not well defined and low anesthetic index → Needs experience.
3- Weak Analgesic: Add Nitrous Oxide (Halothane 68% + N_2O 32% → *Azeotrope* mixture).
4- Weak Muscle Relaxant: Use N-M blocker e.g. Vecuronium.
5- Cardiotoxic:
   a- Stage 1: ↑ Vagal tone → Bradycardia & Heart block → Pretreat by *Atropine*.
   b- Stage 2 → Sensitizes myocardium to catecholamines → Arrhythmia # Propranolol.
   c- Stage 3 → Direct myocardial depressant.
6- Hepatotoxic:
   a- 30% Halothane $\xrightarrow{CYP2E1}$ Tri-fluoro-acetic acid → ? Antigenic → Heptotoxic.
   b- Disulfiram → ↓ CYP2E1 → ↓ Hepatotoxicity of halothane.
   c- Avoid by Low fat & high CHO diet, Vit B_{12} & Methionine.
7- ↓ Respiration (↓RC).
8- Uterine relaxant and # oxytocic effect of ergometrine & oxytocin.
9- Idiosyncrasy: Malignant hyperthermia. Treat by IV Dantrolene.

* Precautions & Contraindications of Halothane:

1- Premedication with Atropine to # ↑ Vagal tone.
2- Do not use:
   a- Parasympathomimetics → Severe bradycardia in stage 1.
   b- Catecholamines → Arrhythmia in stage 2.
   c- Trimethaphan or Curare → Severe Hypotension.
3- Avoid in Liver disease and during labor.

2- *Isoflurane:* Similar to Halothane.

* Advantages:

1- MAC (1.2 %) & Blood / Gas PC (1.4) → Rapid induction & Recovery.
2- Adequate Analgesia & Muscle relaxation → Reduce the dose of N-M blockers.
3- Less Cardiotoxic, Hepatotoxic (2% metabolized), Nephrotoxic & Uterine relaxant.

* Disadvantages:

1- Very expensive.
2- Irritant on bronchi.
3- VD of small coronaries → Steal phenomenon → Precipitate ischemic heart disease.

3- *Enflurane:* Similar to halothane

1- MAC (1.6 %) & Blood / Gas PC (1.8) → Rapid Induction & Recovery.
2- Good muscle relaxation → Reduce dose of N-M blocker.
3- Prolonged use → Release of inorganic ***Fluoride ions*** → Nephrotoxicity.
4- May cause Epilepsy like syndrome → ***Seizures***.

4- *Desflurane:* Similar to Halothane

1- MAC (6 %) & Blood / Gas PC (0.45)
2- Extremely rapid induction & recovery
   Excellent control of anesthetic depth & recovery. Useful in Day-case surgery.
3- Adequate muscle relaxation → Reduce dose of N-M blocker.
4- Negligible metabolism → No Hepatotoxicity or Nephrotoxicity.
5- Irritant to bronchi.

5- *Sevoflurane:* Similar to Halothane

1- MAC (2 %) & Blood / Gas PC (0.65).
2- Extremely rapid induction & recovery.
   Excellent control of anesthetic depth & recovery. Useful in Day-case surgery.
3- Adequate muscle relaxation → ↓ Dose of N-M blockers.
4- Less irritant to bronchi than Desflurane.
5- 3% Deflourinated in liver → Release of ***Fluorine ion*** → Kidney.
6- Interacts with Soda lime.

6- Methoxyflurane:

1- Colorless volatile liquid with sweet odor & Non-inflammable.
2- Highly potent anesthetic (MAC = 0.16%).
3- Excellent Muscle relaxant and Analgesic.
4- NO uterine relaxation → Allowed as obstetric analgesic.
5- Hypotensive and sensitizes myocardium to catecholamines.
6- Nephrotoxic → postoperative diuresis.
Its metabolism → Release fluoride ion → Toxic to distal convoluted tubules.

7- Trichloroethylene:

1- Non-inflammable. Boiling point 87°C.
2- Potent Analgesic → Useful in Obstetric analgesia & Trigeminal neuralgia.
3- In closed circuit method: Trichloroethylene + Soda lime → Dichloroacetylene → Spontaneously explosive and neurotoxic to cranial nerves specially trigeminal.

8- Ethyl Chloride:

1- Inhalation → General Anesthesia But → Inflammable, explosive, irritant → Laryngospasm, cardiotoxic & hepatotoxic.
2- Spry → Freezing → Local Anesthetic used to incise an Abscess But → Pain, difficult incision & Delays healing.

9- Diethyl Ether (Ether):

* Advantages:

1- Cheap.
2- Stages are well defined & high anesthetic index → Easy to apply.
3- Potent Analgesic & Potent Sk.m. relaxant → Use only 1/3 dose of N-M blockers.
4- Not Cardiotoxic, NOT Hepatotoxic & NOT uterine relaxant.

* Disadvantages & Contraindications:

1- Pungent odor.
2- Unstable → Toxic aldehydes & peroxides. Store in dark bottle in a cool place.
3- Inflammable & Explosive → NOT use cautery or diathermy.
4- Highly soluble in blood → Slow induction (induce by IV Thiopentone) & Slow recovery + Postoperative vomiting (use Carbogen).
5- Irritant → Bronchospasm & ↑ Bronchial secretions (use Atropine) → NOT in Bronchial asthma.
6- ↑Glycogenolysis → Hyperglycemia → NOT in Diabetes mellitus.
7- Acidosis especially in children → NOT in acidosis.
8- Convulsions in febrile children:
Treat by → Stop Ether + Carbogen + IV Thiopentone → NOT in febrile children.
9- Na^+ & Water retention & K^+ depletion.
10- ↑ ADH → Oliguria.

9- Nitrous Oxide (N_2O = Laughing Gas)

* Characteristics:

1- Colorless *Gas* of Sweet odor.
2- Blood/Gas partition coefficient = 0.47
3- Weak Anesthetic:
   a- 100% N_2O → Rapid *Light* anesthesia. If used more than 2 minutes → Hypoxia.
   b- 80% N_2O + 20% O_2 → Analgesia *But* inadequate Anesthesia & Muscle relaxation.
   c- 35% N_2O → Analgesia *But No* Anesethia.

* Advantages:

1- Non-inflammable, Non-Explosive & Non-Irritant.
2- Rapid induction (20-30 seconds, Patient is gay & joyful) & Rapid recovery.
3- Good Analgesia in sub-anesthetic concentration (35 %):
   a- Minor operations e.g. dental.
   b- Obstetric analgesia.
   c- Supplement poor analgesic anesthetics e.g. Halothane & Thiopentone.
4- Safe on Respiration, CVS & Vital organs provided no hypoxia.

* Disadvantages of Nitrous Oxide:

1- Supports combustion.
2- Weak anesthetic.
3- Weak muscle relaxant.
4- Not used in presence of closed-air filled spaces e.g. obstructed middle ear, intestinal obstruction, collection of air in pleura, peritoneum or pericardium → Diffusion of N_2O from blood → Expansion of these spaces.
5- Diffusion hypoxia: During recovery → Rapid diffusion from Blood to alveolar air → Prevent the access of oxygen
6- Post-operative excitation.
7- Megaloplastic anemia & Teratogenic to patient and doctor so use extraction system and closed circuit.

Intravenous Anesthesia

* Characteristics:

1-Easy & simple administration.
2- Rapid smooth induction without excitation
   Rapid recovery without post-anesthetic vomiting.
3- No irritation to respiratory tract.
4- No hazards of inflammation or explosion.
5- However, once injected → Can not be withdrawn.

1- *Ultrashort Acting Barbiturates:*

* Preparations:

1- Thiopentone:
   a- I.V. → Fresh solution 2.5%, 6 – 10 ml in 30 seconds, maximum 1 g.
   b- Rectally → Fresh 10% solution, 40 mg/kg ½ hour before operation → Basal anesthesia
2- Hexobarbitone:
3- Methohexitone:
   Similar to thiopentone but more rapid recovery → Useful in outpatients.

* *Pharmacokinetics:*

1- Administered IV & Rectally.
2- Distributed all over the body and passes
   a- BBB & concentrated in brain (Rich in lipid & blood supply).
   b- Placental barrier → ↓ Fetal RC → Neonatal asphyxia.
3- Fate: REDISTRIBUTION from brain to other organs.
   Repeated injections → Tissue saturation → CNS Cumulation → Longer duration → Not suitable to maintain anesthesia.

* *Pharmacodynamics:* See Barbiturates in CNS.

* *Therapeutic Uses:*

1- IV as Induction or Full anesthesia for short operations.
2- Rectally as basal anesthesia.
3- Anticonvulsant in Febrile convulsions in children & Status epilepticus.

* *Disadvantages of Thiopentone:*

1- Prolonged hangover.
2- Poor analgesia and muscle relaxation.
3- Not suitable for maintenance.
4- Hypotension → ↓ Heart, ↓ VMC & VD.
5- Respiratory depression and laryngospasm.
6- *Very Irritant*:
   a- IV concentrated (5%) → Thrombophlebitis.
   b- Extravasation → Slough and necrosis.
   c- Into nerve → Permanent paralysis.
   d- Intra-arterial → Severe VC, thrombosis & gangrene. Management:
      - Procaine or Lidocaine without adrenaline.
      - Heparin followed by oral anticoagulants.
      - VD e.g. α-blockers and even brachial plexus block.
      - Surgical removal of the thrombus.
      - Cooling of the limb.
7- Precipitation of acute Porphyria.
8- Thiopental (Highly Alkaline) is *NOT* mixed with Succinylcholine (Acidic).

2- *Ketamine:*

1- Related to phencyclidine, a hallucinogenic agent.
2- Blocks N-Methyl-D-Aspartate (NMDA)-receptor, an excitatory glutamate receptor.
3- Dissociative Anesthesia → Patient is dissociated from environment → Does not respond to external stimuli, with Analgesia, Amnesia & Stupor.
4- Used IV or IM mainly in Children e.g. in circumcision and burns.
5- Cocaine like effect → ↑ Catcholamines → ↑ Heart rate & ↑ Blood pressure.
6- ↑ IOP, ↑ ICP & ↑ Muscle tone. **(↑ 6)**
7- ***Emergence Phenomenon***: Vivid dreams and hallucination during surgery & recovery. Prevented by premedication with IV diazepam.
8- *Contraindications*:
   a- Labor : Patient is NOT cooperative. b- Mental disorders.
   c- Heart disease and hypertension. d- Glaucoma. e- ↑ ICP.

3- *Neurolept Analgesia:*

1- Thalamonal or Innovar → Mixture of:
   a- Droperidol → Major tranquilizer → Sedation & Psychic indifference +
   b- Fentanyl → Opioid Analgesic → Very potent Analgesic.
2- The emetic effect of Fentanyl is # by the antiemetic effect of Droperidol.
3- Useful in Obstetric Analgesia & Endoscopy → ***Patient is cooperative***.
4- Large Doses:
   a- Fentanyl → ↓ R.C. # Naloxone.
   b- Droperidol → Acute Parkinsonism # Atropine.
5- *Neurolept Anesthesia* = Droperidol + Fentanyl + N_2O 65%

4- *Propofol:*

1- Phenol derivative.
2- ↑ GABA-A transmission.
2- Rapid induction & Rapid recovery (4 minutes after the last dose).
3- Used for induction, also can be used for maintenance by IV infusion.

5- *Benzodiazepines:*

1- Preparations:
   a- Diazepam: 10-40 mg Slow I.V. → Induction and Basal anesthesia.
   b- Lorazepam.
   c- Midazolam → Quickest, shortest & least irritant.
2- Useful in uncomfortable procedures e.g. endoscopy & Cardiac catheterization. In painful ones add an analgesic.
3- Irritant → Pain and thrombophlebitis.

6- Opioid Analgescis:

1- I.V. Morphine (1-3 mg / kg) or Fentanyl (50-100 ug).
2- Certain cases of cardiac surgery/

7- Propanidid:

1- IV Anesthesia of Short duration. Metabolized by Pseudo-Cholinesterase.
Its action is potentiated and prolonged by Anti-Ch.E. e.g. Neostigmine.
2- Used to substitute barbiturates in patients allergic to them or with Porphyria.

8- Etomidate:

1- Advantages → Rapid short anesthesia & Minimal Respiratory & CVS effects.
3- Disadvantages → Pain at site of injection & ↑ Muscle movement during induction

9- Althesin:

1- Steroid anesthetic.
2- Rapid metabolism → Rapid short anesthesia.
3- Side effects: a- Hypotension. b- Muscle twitches.
4- Contraindications: Patients with liver disease.

✂✂✂✂✂✂✂✂✂✂✂✂✂✂✂✂✂✂✂

Basal Anesthesia

1- State of light anesthesia not deep enough to permit surgical operations.
2- Used mainly as pre-anesthetic medication.
3- Examples :
a- Diazepam 10-40 mg SLOW IV.
b- Thiopentone 10% fresh solution Rectally, 40 mg/kg.
c- Paraldehyde 15 ml of 8% solution Rectally.

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NB) Balanced Anesthesia:

Combinations of drugs → Make advantage of each drug & ↓ adverse effects.

	Anesthesia	Analgesia	Muscle Relaxation	Sedation & Amnesia
1- Halothane	Strong	Weak	Weak	---
2- N_2O	Weak	Strong	Weak	---
3- Vecuronium	---	---	Strong	---
4- Diazepam	Help	---	Help	Strong

Pre-anesthetic Medication

Preparation of the patient for surgery by:

1- Full physical Examination & Laboratory investigations:

a- Physical examination of chest, heart, Bl.p., H.R. etc.
b- Investigations: X-ray & E.C.G., Kidney & liver function tests, blood sugar, Blood group, coagulation time, etc.

2- Night of operation: Light super, purgative & shaving of operation site.
Morning of operation: No breakfast.

3- **Pre-anesthetic Medication Proper**:

Aim of pre-anesthetic medication is to provide:

a- Smooth induction and recovery without vomiting if possible.
b- Sedation, tranquillity and amnesia } to ↓ amount of anesthetic required
c- A n a l g e s i a . } and hence its toxicity.
d- ↓ Parasympathetic tone → ↓ Secretions, ↓ Bronchospasm & Laryngospasm & protect heart from ↑ vagal tone → ↓ Post-operative complications.

A) Sedatives & Hypnotics:

** Advantages:*

1- Diminish anxiety and excitement → ↓ Amount of anesthesia → ↓ Its toxicity.
2- Shortens induction.
3- Promote sleep after the operation.

** Preparations:*

1- Short Acting Barbiturates e.g. Pentobarbitone or Secobarbital 100-200 mg orally at night of operation and 1-2 hours before the operation.
2- Non-barbiturates: Diazepam, Chloral hydrate, Paraldehyde & Antihistaminics.

B) Tranquilizers:

1- Example: Chlorpromazine 50 mg at night or 1-2 hours before the operation.
2- Advantages: a- Sedative. b- Hypothermic. c- Anti-emetic.

C) Narcotic Analgesics:

1- Morphine: 10-15 mg SC one hour before the operation →

A) Advantage: 1- Analgesia. 2- Sedation and amnesia.

B) Disadvantages:

1- Delay awakening from anesthesia. 2- ↓ R.C. & ↓ Cough center.
3- PPP → Interferes with staging of anesthesia. 4- Nausea and vomiting.
5- Bronchospasm. 6- Postoperative constipation and retention of urine.
7- Biliary and urinary spasm. 8- Neonatal asphyxia.
9- Acute toxicity. 10- Addiction.

2- Meperidine (Pethidine) : 50-150 mg Orally or IM

a- Analgesic.

b- Better than Morphine → Less ↓ RC, Less emetic & Atropine like → NO Constipation or PPP.

3- Others: Pentazocine & Fentanyl.

D) Parasympatholytics:

Atropine	Hyoscine (Scopolamine)	Glycopyronium
1- Natural tertiary amine.	1- Natural tertiary amine.	1- Synthetic Quaternary ammonium compound.
2- ↑ CNS → Excitation.	2- ↓ CNS → Sedation & Amnesia	2- Little C.N.S.
3- Anti-emetic.	3- More Anti-emetic.	
4- ↑ R.C.	4- More ↑ R.C.	
5- Bronchodilator.	5- Bronchodilator.	
6- ↓ Bronchial & Salivary secretions	6- More Antisecretory.	3- ***Good Antisecretory***.
7- Tachycardia.	7- No tachycardia.	4- No Tachycardia.
8- Dose : 1 mg IM	8- Dose 0.3-0.6 mg S.C.	5- Dose 0.4 mg IM.
		6- Longer duration.

	MORPHINE	ATROPINE
1- R.C. :	↓ R.C.	↑ R.C.
2- Emesis :	Emetic	Antiemetic
3- Eye :	p. p. p.	Mydriasis
4- Salivation :	↑	↓
5- Bronchi :	Spasm	Dilatation
6- Heart :	↑ Vagal tone → Bradycardia	↓ Vagal tone → Tachycardia
7- smooth m. :	Spasmogenic	Spasmolytic.

* *Disadvantages of Atropine:*

1- Tachycardia → Harmful Thyrotoxicosis & Pheochromocytoma and with anesthetics that sensitize the heart (Hyoscine & Glycopyrronium are Better).
2- Excessive drying of bronchial mucus and ↓ ciliary movement → ↓ Expulsion of sputum and foreign bodies.
3- Post-operative abdominal distention, constipation and paralytic ileus.
4- Post-operative retention of urine specially in enlarged prostate.

E) Basal Anesthesia: Thiopentone, Diazepam & Paraldehyde.

F) Anesthetic Adjuvant:

1- N-M Blockers:
   a- Succinyl choline for endotracheal intubation.
   b- Curare and similar agents for maintenance.
2- Hypothermia eg Chlorpromazine in operations with interrupted circulation eg cardiosurgery.
3- Controlled hypotension: Trimethaphan & Sodium Nitroprusside in neuro- and plastic surgery.
4- Vasopressors for hypotension. 5- Anti-arrhythmics e.g. Lidocaine.

Local Anesthetics (L.A.)

* Classification of L.A. According to Chemistry:

Local Anesthetic	Potency	Duration	Remarks
A) *Natural Bezoic Acid Ester*: Metabolized by Pseudo-Ch.E. • **Cocaine**	2	Medium	Topical use Only e.g. Eye
B) *Synthetic PABA Esters*: Metabolized by Pseudo-Ch.E. → PABA → Allergy & Antagonize Sulfonamides			
1- Procaine *(Novocaine)*	1	Short	Infiltration *But Not* Surface (Topical)
2- Tetracaine *(Amethocaine)*	16	Long	Infiltration & Surface (Topical)
3- Benzocaine			Surface only
C) *Synthetic Amides*: Metabolized by Hepatic Microsomal Enz.			
1- Lidocaine *(Xylocaine & Lignocaine)*	4	Medium	Anti-arrhythmic
2- Mepivacaine *(Mepacaine & Carbocaine)*	2	Medium	Longer than lidocaine
5- Prilocaine *(Citanest)*	3	Medium	Longer than Lidocaine + Met-Hb
3- Bupivacaine *(Marcaine)*	16	Long	Longer than Lidocaine
4- Etidocaine *(Duranest)*	16	Long	Longer than Lidocaine
6- Ropivacaine *(Naropin)*	16	Long	Longer than Lidocaine
7- Dibucaine *(Cinchocaine & Nupercaine)*			Extremely Potent & Toxic → Topical use mainly

* Classification of L.A. According to Solubility & Use:

A) Soluble L.A.

I- L.A. Suitable for Injection & Surface Anesthesia *(Except Procaine)*:

1- Procaine *(Infiltration But Not Surface anesthesia)*
2- Tetracaine 3- Lidocaine 4- Dibucaine

II- L.A. for Topical use ONLY e.g. eye:

1- Cocaine 2- Phenacaine 3- Butacaine

B) Insoluble L.A. for surface anesthesia e.g. powder & ointment for wounds & ulcers:

1- Benzocaine 2- Orthoform

* Kinetics of L.A.:

1- Pass easily mucous membranes *Except* Procaine
2- Pass B.B.B. & Placental barrier
3- Metabolism:
   a- Esters → Metabolism of Pseudo-Ch.E.
      PABA Esters → PABA → Allergy & Antagonize the anti-bacterial effect of Sulfa
   b- Amides → Hepatic microsomal enzymes
4- Excretion in urine. Acidification of urine → ↑ Their renal excretion

* Dynamics of L.A.:

1- ***Local Anesthetic Action***:
   a- **Mechanism**: L.A. block voltage dependent Na^+-channels from inside the nerve fiber. The Free Non-Ionized (Non-Dissociated) base passes neuronal membrane → Inside nerve → Ionized (Active form) → Block Na^+-channel → Membrane stabilization → ↓ Impulse generation & Propagation.
   b- **Intra-cellular pH** → More acid by CO_2 → More ionization of base → More active.
   c- **Extra-cellular pH** → Acidity e.g. Inflammation or Abscess → Ionization of Base → Not lipid soluble → Can Not pass inside nerve → Inactive.
   d- Extra-cellular **cations**: ↑ Ca^{2+} → ↓ Activity while ↑ K^+ → ↑ Activity of L.A.
   e- Addition of **Hyaluronidase** enzyme → ↑ Spread of L.A. → ↓ Duration & ↑ Toxicity.
   f- Addition of **Adrenaline** → V.C. → ↓ Absorption of L.A. → ↓ Spread → ↑ Duration, ↓ Toxicity & ↓ Bleeding.
   g- **Sequence**: Smaller fibers before larger & demylinated before myelinated fibers. Sympathetic & Pain → Temperature → Touch & Pressure → Motor fibers
   h- **Recovery** → Reverse direction.

2- **C.N.S.** → Stimulation (Especially Cocaine) followed by depression.

3- **↓ Release of A.Ch.** → Ganglion Block & Neuro-Muscular Block.

4- **C.V.S.**:
   a- *Cocaine* → Initial bradycardia (Initial ↑ C.I.C.) *Then* Tachycardia, V.C. & ↑ Bl.p. (Cocaine → ↓ Neuronal Uptake-1 & MAO-inhibitor → ↑ Catecholamines).
   b- *Other L.A.* → Direct cardiac depressant + V.D. + ↓ Bl.p. (Add Adrenaline)
   c- *Procaine & Lidocaine* have Anti-Arrhythmic effect.

5- **Smooth muscle** → Spasmolytic effect.

* Methods of Administration of L.A.:

1- **Surface or Topical** on skin or mucous membrane *(Not* Procaine)
2- **Infiltration S.C.** → Nerve endings
3- **Nerve block** → In the vicinity of a major nerve trunk e.g. brachial plexus
4- **Sympathetic block** → Around sympathetic ganglia
5- **Paravertebral block** → Around spinal routes
6- **Spinal** Anesthesia in Subarachnoid at Lumbar 3-4: All *But Not* Cocaine
   The level of spinal anesthesia can be determined by the specific gravity of L.A. compared to C.S.F. (Isobaric, Hypobaric & Hyperbaric) & position of the patient.
7- **Epidural** → Epidural space

* Toxicity of L.A.:

1- **Allergy** especially PABA Esters
2- **C.N.S. Stimulation**: Prevented by pre-medication with Diazepam or a Barbiturate
3- **C.V.S.** → Bradycardia, V.D. & Hypotension → Collapse. Give I.V. fluids + Vasopressor
4- Prilocaine → **Met-hemoglobinemia**.
4- Complications of **Spinal Anesthesia**:
   a- C.V.S.: Block Sympathetic → ↓ H.R. + V.D. + ↓ Bl.p. → Shock & Cardiac arrest
      Management → Tilt the head down + I.V. Fluids + Vasopressors
   b- Respiratory paralysis due to high spinal anesthesia → Thoracic (Intercostal muscles) then cervical (Diaphragm) then Medullary R.C.
   c- Neurological → Trauma, Irritation & Headache

NB) Other Methods to Produce Local Anesthetic Effect:

1- Intra-thecal or Epidural injection of **Opioid** analgesics e.g. Morphine.
2- **Application of Cold**:
   a- *Spray of Ethyl Chloride*: Useful in Abscess incision.
   b- *Refrigeration* of a limb before its amputation
3- Rendering tissue **anemic** by Tourniquet
4- **Paralysis** of Sensory Nerve Ending of Fiber:
   a- *Protoplasmic poisons* e.g. Phenols & Quinine → Initial irritation then anesthesia.
   b- *Astringents* e.g. Ethyl alcohol in trigeminal neuralgia
   c- *Obtundents* e.g. Clove oil & Zinc chloride in Toothache.

Cocaine

Natural Benzoic acid ester alkaloid of Erythroxylone coca leaves.

* Kinetics of Cocaine:

1- Well absorbed from All sites including mucous membranes
2- Distributed Al over the body & passes B.B.B. & Placental barrier
3- Partially Metabolized by Pseudo-Ch.E.
4- Excreted in urine partially unchanged

* Dynamics of Cocaine:

A) Mechanism of Action:

1- **Local anesthetic** → Blocks neuronal Voltage dependent Na^+-channels → Neuronal membrane stabilization.
2- **Accumulation of Catecholamines in C.N.S. & Periphery**:
   a- Mainly ↓ Neuronal Uptake-1 of Catecholamines
   b-MAO inhibitor effect

B) Actions of Cocaine:

1- **Local anesthetic**: Used as Surface anesthesia ONLY

2- **C.N.S.** → ↑ Dopamine & Noradrenaline → POWERFUL ↑ CNS in a descending manner:
   a- Cortex → Euphoria, Elation, ↑ Mental alacrity, Wakefulness, ↑ Capacity to work & Anti-fatigue. Work is accelerated *BUT Less* accurate than with caffeine
   b- Sub-cortex → ↑ R.C., ↑ V.M.C., ↑ C.I.C., ↑ C.T.Z. & ↑ H.R.C. → Hyperthermia
   c- Spinal cord → ↑ All spinal reflexes

3- **Skeletal muscle** → Anti-fatigue effect (Central mechanism)

4- **Potentiate Sympathomimetics** (↓ Uptake-1 & MAO inhibitor).

5- **C.V.S.**:
   a- Initial bradycardia (↑ C.I.C.)
   b- *Then* Tachycardia + V.C. + Hypertension (↑ Catecholamines & ↑ V.M.C.)
   c- No need to add Adrenaline

6- **Eye**:
   a- Loss of sensory reflexes e.g. Corneal & Conjunctival reflexes
   b- ↑ Endogenous Noradrenaline → Active mydriasis (preserve light reflex) + Decongestion

* Cocaine Poisoning:

A) Acute Cocaine Poisoning:

1- Manifestations:

a- **C.N.S.** → Marked stimulation → Excitation, Psychosis, Hyperpyrexia & Convulsions *Followed* by C.N.S. depression → Coma & ↓ R.C. → Cause of death
b- **C.V.S.** → Tachycardia, Arrhythmia & Hypertension

2- Management:

a- Artificial respiration
b- Chlorpromazine (Dopamine antagonist) → Treat excitation & Psychosis
c- Diazepam → For convulsions
d- α-Blocker for Hypertension + β-Blocker for tachycardia & arrhythmia → Labetalol.

B) Cocaine Dependence:

1- **No** Tolerance
2- Severe **Psychic** dependence → Toxic psychosis
3- The use of purified cocaine preparations e.g. Cocaine HCl Snuff (Snow) & Cocaine base Smoking (Crack) → Psychic & Physical dependence → **Addiction** with classic withdrawal manifestations.
4- **Management**:
   a- Gradual withdrawal of cocaine in especial hospital (sanatorium).
   b- Substitution with Tricyclic anti-depressants (Cocaine like action).

Pharmacology

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Part 2

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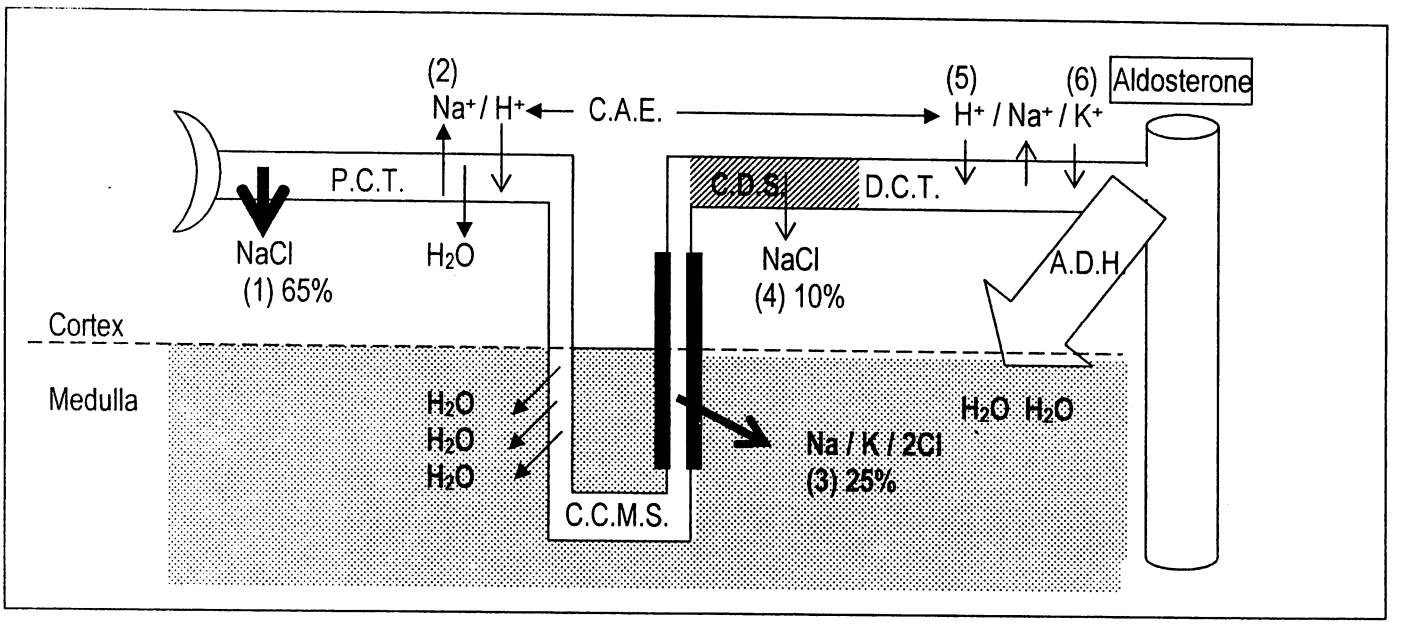
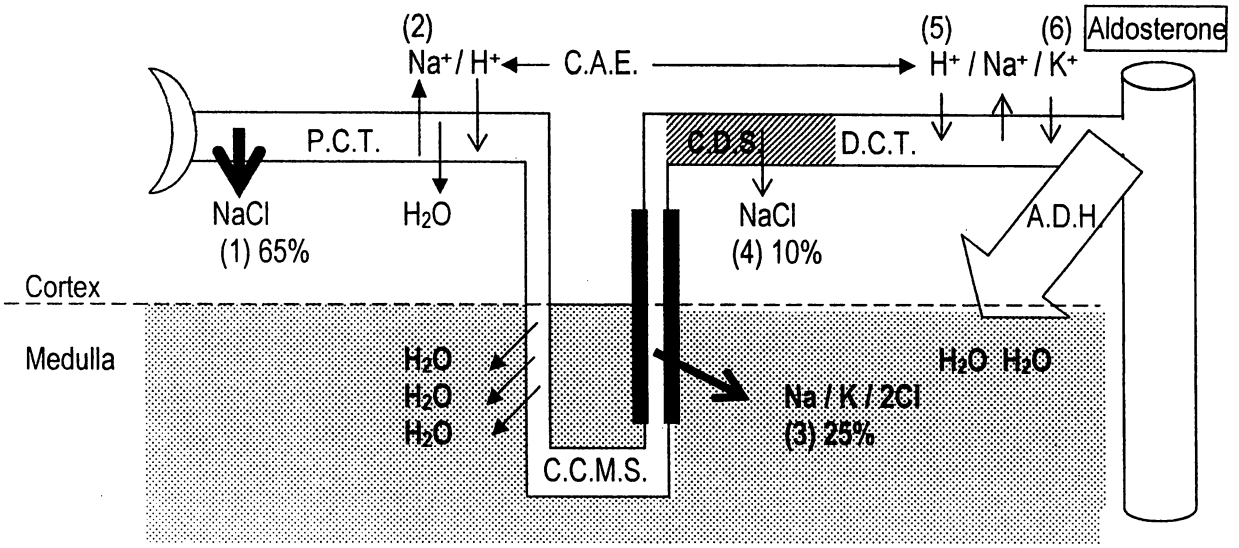
Diuretics





Physiology Of The Kidney

A) Glomeruli:

1- Hydrostatic pressure in Afferent Arteriole = + 75 mm Hg
2- Osmotic pressure of plasma Albumin = -- 25 mm Hg
3- Hydrostatic pressure in Bowman's Capsule = -- 5 mm Hg
4- Net filtering pressure = + 45 mm Hg
5- Renal Blood Flow (RBF) = 1300 ml / min = 1/4 C.O.P.
6- Glomerular Filtration Rate (G.F.R.) = 125 ml / min = 180 Liter / day.
7- Only 1 -2 liters of urine is excreted / day = About 99% of filtrate is reabsorbed. So the kidney can be considered as a Reabsorbing organ mainly.

B) Proximal Convoluted Tubules (PCT):

1- Site I: Most of filtered NaCl (About 65%) is Actively reabsorbed
2- Site II: Some Na^+ is reabsorbed in exchange for H^+ under the effect of Carbonic Anhydrase Enzyme (CA.E.)
3- Na^+ is reabsorbed with its iso-osmotic water = Obligatory water reabsorption.
4- Filtrate is isotonic.
5- Most of filtered K^+, Glucose & amino-acids are reabsorbed.
6- Organic acids & bases are Reabsorbed & Secreted in P.C.T. e.g. Uric acid, penicillin, Diuretics & Probenecid.

C) Descending Loop Of Henle:

- Freely filterable to Water = Free Water reabsorption → Filtrate is hypertonic.

D) Medullary Part of Thick Ascending Loop Of Henle:

1- Site III: Na^+ / K^+ / 2 Cl^- Symport (Co-transport) about 25% of filtered Na^+ under the effect of Na^+/K^+ ATPase enzyme.
2- Impermeable to water → Filtrate is Hypotonic.
3- Medulla is Hypertonic → Imbibe water from Descending loop of Henle & D.C.T. & Collecting Tubules → Counter-current Multiplier System (C.C.M.S.).

E) Distal Convoluted Tubules (D.C.T.) & Collecting Tubules:

1- Site IV: Early part of D.C.T. = Cortical Diluting Segment → Active Reabsorption of about 10% of Filtered NaCl.
2- Late part of D.C.T. → Compensatory Na^+ Reabsorption → Limited Capacity (3-5%):
   a- Site V: Na^+ / H^+ Exchange under the effect of C.A.E.
   b- Site VI: Na^+ / K^+ Exchange under the effect of Aldosterone
3- Late Part of D.C.T. & Collecting tubules → Reabsorb water under the effect of A.D.H. = Facultative water reabsorption.

Diuretics

Drugs that increase the volume of urine by increasing water & solute excretion.

* Classification:

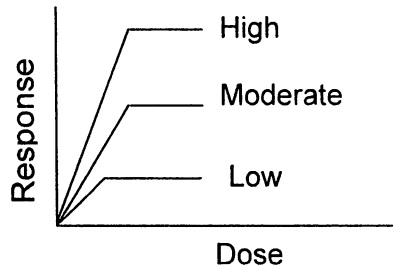
I- Extra-Renal (Pre-Renal):

1- Water & Ethyl Alcohol → ↓ Release of ADH → ↓ Facultative water reabsorption.
2- Digitalis ONLY in cases of Heart Failure → +ve Inotropic → ↑ C.O.P. → ↑ R.B.F.
3- Albumin ONLY in cases of Hypoalbuminemia → Restore osmotic pressure of plasma → ↑ Blood volume → ↑ R.B.F.
4- Dobutamine (↑ C.O.P.) & Dopamine (↑ C.O.P. & Renal V.D. → ↑ R.B.F.).
5- Methylxanthines eg Theophylline → ↑ COP & Renal VD → ↑ RBF + Renal effect.

II- Renal:

A) Natriuretics = Saluretics:

They ↓ Na^+ reabsorption from the nephron → ↑ Na^+ excretion in urine with its iso-osmotic (obligatory) water → ↑ Volume of urine.



1- High Efficacy (High Ceiling) = Loop Diuretics:

a- They act mainly on the Medullary part of thick ascending loop of Henle → ↓ C.C.M.S.
b- Examples: Frusemide & Ethacrynic acid.

2- Moderate Efficacy Diuretics:

a- They act mainly on the cortical diluting segment.
b- Examples: Thiazide diuretics & Thiazide analogues.

3- Low Efficacy Diuretics:

a- Carbonic Anhydrase Inhibitors e.g. Acetazolamide.
b- Potassium Retaining (Sparing or Conserving) Diuretics:
  a- Aldosterone Antagonists e.g. Spironolactone.
  b- Non-Aldosterone Antagonists e.g. Triamterene & Amiloride.

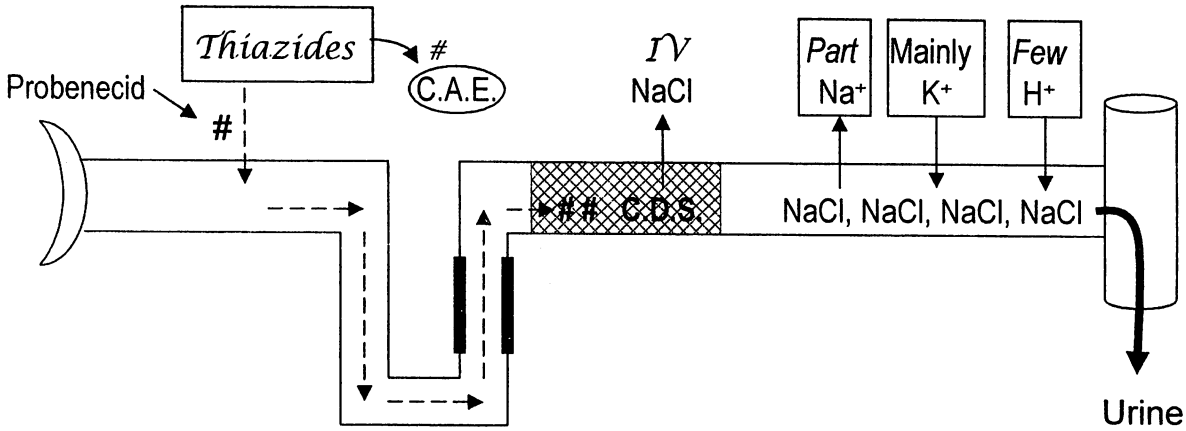
B) Osmotic Diuretics e.g. Mannitol

C) Acidifying Diuretics e.g. Ammonium Chloride.

N.B.)

1- In the exam. Mention the Name of the site & NOT its number.
2- Diuretics in common use:
  a- Thiazide & their analogues.
  b- Loop diuretics.
  c- Potassium retraining diuretics.
  d- Mannitol.
3- Self-Limiting Diuretics: Acetazolamide & Ammonium chloride → Acidosis.

I - Thiazide Diuretics (Benzothiadiazines)



Urine	Blood
1- ↑ Water → Diuresis	→ Hypovolemia
2- ↑ Na^+ → Natriuresis	→ Hyponatremia
3- ↑ Cl^- → Chloruresis	→ Hypochloemia
4- ↑ H^+ → Acid urine	→ Alkalosis
5- ↑ K^+ → Kaluresis	→ ***Hypokalemia***
6- ↑ Mg^{2+}	→ Hypomagnesemia
7- ↓ Ca^{2+}	→ ***Hyper***calcemia

* Pharmacodynamics:

1- Diuretic Effect:

1- Thiazide diuretics MUST be secreted in P.C.T. to act from inside the nephron. Probenecid inhibits this secretion → Antagonize the diuretic effect of thiazides.

2- They act MAINLY on the early part of D.C.T. (Cortical Diluting Segment) → Inhibit NaCl reabsorption (About 10%).

3- Some Thiazides e.g. Chlorothiazide → Weak ↓ Carbonic Anhydrase enzyme by their sulfonamide radical (*Not essential for the diuretic effect).*

4- Excess NaCl will reach the late part of D.C.T., where PART of Na^+ is reabsorbed in exchange for K^+ mainly & some H^+.
The remaining Na^+ will be excreted in urine with its iso-osmotic water →

* Urine:	* Blood:
a- Excess Water → Moderate Efficacy Diuresis	→ Hypovolemia
b- Excess Sodium → Natriuretic effect	→ Hyponatremia
c- Excess Chloride → Chloruretic effect	→ Hypochloremia
d- Some Hydrogen → Acid urine	→ Alkalosis
e- Excess Potassium → Kaluretic effect	→ ***Hypokalemia***
f- Excess Magnesium	→ Hypomagnesemia
g- Less Calcium	→ ***Hyper***calcemia

5- Thiazides ↓ R.B.F. & ↓ G.F.R. → They ***NOT*** indicated in renal insufficiency. Thiazides lose their diuretic effect when G.F.R. < 20 ml / minute.

2- *Anti-diuretic Effect:*

1- Only in Nephrogenic Diabetes Insipidus = Insensitivity to A.D.H.
2- May be due to ↓ G.F.R.

3- *Antihypertensive Effect:*

1- Thiazides are effective Anti-hypertensives even in sub-diuretic doses.
2- Mainly due to *Direct Arteriolar V.D.*:
   a- ***K^+-channel opener*** → Hyperpolarization.
   NB) Diazoxide → Thiazide → Non-diuretic *BUT* Direct Arterial V.D.
   b- Depletion of Na^+ & Water from arteriolar wall → N.A. # ↓ Na
   ↓ Edema & ↓ Pressor effect of noradrenaline & angiotensin. A.T. # ↓Water
   c- ***Prostaglandins*** may play a role. NSAID # Antihypertensive effect of Thiazides
3- Diuretic → ↓ Blood volume → Temporary effect & NOT Essential.

4- *Hyperglycemia:* Open K^+-channel → Hyperpolarization → ↓ Insulin release.

5- *Hyperlipidemia:* ↑ Blood Cholesterol & Triglycerides.

6- *Hyperuricemia:* ↓ Uric acid excretion via competition in P.C.T.

* *Therapeutic Uses of Thiazide Diuretics:*

1- **Edema**: ***Cardiac***, Hepatic or Renal.
   Thiazides are useful in Congestive Heart Failure (C.H.F.) due to:
   a- Diuresis → ↓ Blood volume → ↓ V.R. → ↓ E.D.V. → ↓ Pre-load.
   b- Arterial V.D. → ↓ T.P.R. ⟶ ↓ After-load.
2- Mild & Moderate **Hypertension**:
   a- Useful even in use sub-diuretic doses.
   b- Direct V.D. & ↓ Blood volume.
   c- Antagonize edema induced by other Direct V.D. e.g. Hydralazine.
3- Nephrogenic Diabetes Insipidus.
4- Premenstrual Syndrome (P.M.S.) & Premenstrual Migraine.
5- Idiopathic hypercaluria & Renal calcium calculi (stones).
   Useful in Hypocalcemia & Osteoporosis.

* *Adverse Effects & Toxicity of Thiazide Diuretics:*

1- ***Hypokalemia*** → Worsens Digitalis Toxicity, Liver & Kidney insufficiency.
   Hypokalemia can be avoided by:
   a- Intermittent use of least effective dose of the diuretic.
   b- Fruit juice.
   c- KCl supplement. Oral solution is less irritant than tablets.
   d- Add K^+-retaining diuretic e.g. Spironolactone.
2- Hyponatremia. 3- Hypochloremic Alkalosis.
4- Hypomagnesemia. 5- Hypovolemia.
6- Hypercalcemia. 7- Hyperglycemia → Worsen Diabetes mellitus.
8- Hyperlipidemia. 9- Hyperuricemia → Worsens Gout.
10- Hypersensitivity & Cross allergy with other sulfonamides e.g. Antibacterial.
11- Bone marrow inhibition. 12- G.I.T. disturbances. 13- Fetotoxic.

* *Contraindications of Thiazide Diuretics:*

1- Digitalis toxicity (Hypokalemia, Hypomagnesemia & Hypercalcemia).
2- With corticosteroids (Hypokalemia).
3- Advanced liver disease.
4- Advanced renal disease. Thiazides → ↓ R.B.F. & ↓ G.F.R.
5- Diabetes mellitus (Hyperglycemia).
6- Gout (Hyperuricemia).
7- Pregnancy (Fetotoxic).

* *Preparations of Thiazide Diuretics:*

All → Absorbed Orally & Excreted in P.C.T. # Probenecid.

1- Chlorothiazide	500-1000 mg/day	- Water soluble
2- HYDROCHLOROTHIAZIDE *(Hydrex)*	25-100 mg/day	- Rapid excretion
3- Hydroflumethiazide	25-100 mg/day	- Onset 1 hour
4- Bendroflumethiazdie	2.5-15 mg /day	- Short duration 6-12 hs.
5- Trichlormethiazdie	1-4 mg/day	- Lipid soluble
6- POLYTHIAZIDE	1-4 mg/day	- Slow excretion → Long duration 24 hs
7- Cyclothiazide	1-2 mg/day	- Onset 1 hour.

* *Thiazide Analogues:*

Differ from thiazide chemically but similar pharmacology + Long Duration

1- ***Chlorthalidone*** *(Hygroton):* 50 mg/day Long duration

2- ***Indapamide*** *(Natrilix)*: 2.5 mg/day
   a- Calcium channel blocker → Direct arterial V.D.
   b- Used in sub-diuretic dose in treatment of hypertension.
   c- Minimal effect on electrolytes, glucose & uric acid.
   d- Depends on *Biliary* excretion → Safe in renal patients.
   e- Long duration → Effective in a single Oral dose (2.5 mg/day)

3- Clopamide *(Brinerdin)*
4- Xipamide *(Epitens).*
5- Quinethazone
6- Metolazone → Effective even G.F.R. < 20 ml/min

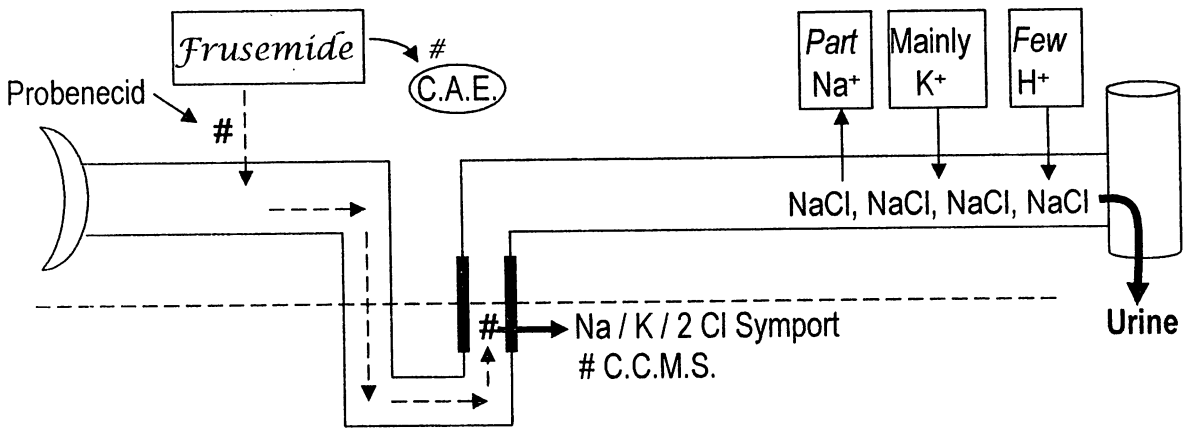
II- Loop Diuretics
"High Efficacy or High Ceiling Diuretics"

1- Sulfonamides: Frusemide, Torsemide, Bumetanide, Piretanide & Mefruside.
2- Non-Sulfonamides: Ethacrynic acid, Indacrinone & Tienilic acid.

1- Frusemide (Furosemide, Lasix):

* Pharmacokinetics:

1- Well absorbed Orally.
2- Extensively bound to plasma proteins → Displaces Warfarin.
3- Hepatic metabolism.
4- Active excretion in P.C.T. # Probenecid → Antagonize its diuretic effect.
5- Prompt (quick) onset & Short Duration:
   a- Orally (20 – 80 mg) → Onset 15 - 30 minutes & Duration 4 - 6 hours
   b- I.V. (20 – 40 mg) → Onset 2 – 10 minutes & Duration 2 - 3 hours.



* Pharmacodynamics:

1- Diuretic Effect:

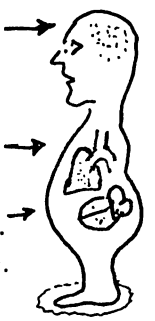
1- Powerful (High efficacy), Prompt onset & Short Duration.
2- Frusemide *Must* be excreted in PCT to act from inside Nephron # Probenecid.
3- Acts *Mainly* on the Medullary Part of Thick Ascending Loop of Henle → ↓ Na^+ / K^+ / 2 Cl^- Symport (Co-transport, about 25% of filtered Na^+) → ↓ Osmolarity of the Medulla → Interfere with Counter-current Multiplier System → Excess water excretion.
4- Large dose → Mild ↓ Carbonic Anhydrase Enzyme (Sulfonamide radical).
5- Excess Na^+ will reach the late part of D.C.T. where a part of Na^+ is reabsorbed in exchange with some H^+ & MAINLY K^+. The remaining Na^+ will be excreted in urine with its iso-osmotic water.
6- The *URINE* will contain ⟶ *Blood*
   a- Excess Water → High Efficacy Diuresis → Hypovolemia
   b- Excess Na^+ → Natriuretic effect → Hyponatremia
   c- Excess Cl^- → Chloruretic effect → Hypochloremia
   d- Excess H^+ → Acid urine → Alkalosis
   e- Excess K^+ → Kaluretic effect → HYPOKALEMIA
   f- Excess Mg^{2+} ⟶ Hypomagnesemia
   g- Excess Ca^{2+} ⟶ Hypocalcemia
7- Frusemide ↑ R.B.F. may be via Prostaglandins # N.S.A.I.D.
   It is effective as a diuretic even when G.F.R. < 10 ml/min.

2- *Antihypertensive effect*: By its diuretic effect, NO direct arterial V.D.
3- *Hyperglycemia* → ↓ Release of Insulin.
4- *Hyperlipidemia* → ↑ Plasma Cholesterol & Triglycerides.
5- *Hyperuricemia* → ↓ Excretion of Uric acid.

* *Therapeutic Uses of Frusemide:*

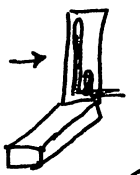
- Powerful & Prompt → Useful in Emergency, Severe & Resistant (Refractory) cases.
- Used Orally & Injection.

1- *Edema:*



a- Emergency Acute Pulmonary Edema = Acute Left Ventricular Failure.
I.V. Frusemide → ↓ Blood volume & *Veno-dilatation* → ↓ V.R. → ↓ EDV → ↓ Preload & ↓ Pulmonary congestion.
b- Cerebral edema. I.V. Frusemide → ↓ Edema & ↓ Pressure on vital centers.
c- Severe or Refractory edema e.g. C.H.F., Liver cirrhosis & Nephrotic syndrome.
Use Oral Frusemide either Alone or + Other diuretic (Thiazide or K^+-Retaining).

2- *Hypertension:*



a- Frusemide lowers Bl.p. by its diuretic effect ONLY, it has NO direct V.D.
b- Emergency Hypertensive Encephalopathy → I.V. Frusemide.
c- Severe & Resistant Hypertension → Oral Frusemide.
d- Hypertension + renal Impairment → Oral Frusemide.

3- *Acute Renal Failure* → Use Large Dose of Frusemide either Oral or I.V.

4- *Hypercalcemia.*

* *Adverse Effects & Toxicity of Frusemide:*

1- ***Hypokalemia*** → Worsens Digitalis Toxicity, and Liver & Kidney insufficiency.
Hypokalemia can be avoided by:
a- Intermittent use of least effective dose of the diuretic.
b- Fruit juice.
c- KCl supplement. Oral solution is less irritant than tablets.
d- Add K^+-retaining diuretic e.g. Spironolactone.
2- Hyponatremia. 3- Hypochloremic Alkalosis. 4- Hypomagnesemia.
5- Hypocalcemia. 6- Hypovolemia, Hypotension & Dehydration.
7- Hyperglycemia → Worsen Diabetes mellitus.
8- Hyperlipidemia. 9- Hyperuricemia → Worsens Gout.
10- Hypersensitivity & Cross allergy with other sulfonamides e.g. Antibacterial.
11- Bone marrow depression.
12- Ototoxicity: Frusemide is toxic to hair cells of inner ear → Hearing defect & ***Deafness*** especially in patients with Renal insufficiency or taking concurrent ototoxic drugs e.g. Gentamicin.
13- G.I.T. disturbances.
14- Fetotoxic.

* Contraindications of Furosemide Diuretics:

1- Digitalis toxicity (Hypokalemia).
2- With corticosteroids (Hypokalemia).
3- Advanced liver disease.
4- Diabetes mellitus (Hyperglycemia).
5- Gout (Hyperuricemia).
6- Pregnancy (Fetotoxic).

* Drug Interactions of Furosemide:

1- Frusemide displaces Warfarin from plasma protein binding sites.
2 - Frusemide ↓ Renal clearance of Lithium carbonate.
3 - Probenecid ↓ Renal tubular excretion of Frusemide.
4 - N.S.A.I.D. → ↓ Diuretic effect of Frusemide.
5- Frusemide → Hypokalemia → ↑ Digitalis toxicity.
6 - Frusemide → ↑ Ototoxicity of Aminoglycosides e.g. Gentamicin.
7 - Frusemide → ↑ Nephrotoxicity & Aminoglycosides & Cephalosporins.

2- Torsemide (Demadex): 10-20 mg/day Orally & I.V.

1- Stronger than Frusemide 3 times.
2- Less excretion of K^+ & Ca^{2+}.
3- Metabolic elimination.

3- Bumetanide (Burinex, 0.5–1 mg Oral & I.V.) → Stronger than Frusemide.

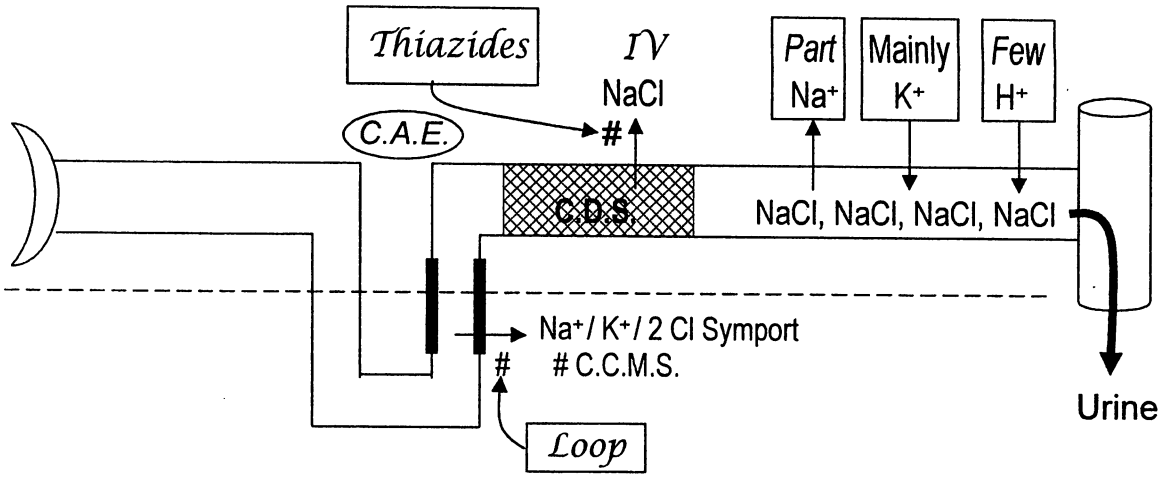
4- Piretenide (Arelix, 6 mg Orally) → Similar to Frusemide + Direct V.D.

5- Ethacrynic acid (Edecrin): 50-150 mg Orally or I.V.

1- Similar to Frusemide, But:
   a- NOT sulfonamide derivative:
      - NOT ↓ Carbonic anhydrase enzyme
      - No cross allergy with other sulfonamides.
   b- Has a uricosuric effect.
   c- More gastric irritation.
   d- More Deafness, may be permanent.
2- Useful in Emergency, Severe & Refractory Edema & Hypertension.

6- Indacrinone: } Similar to Ethacrynic acid

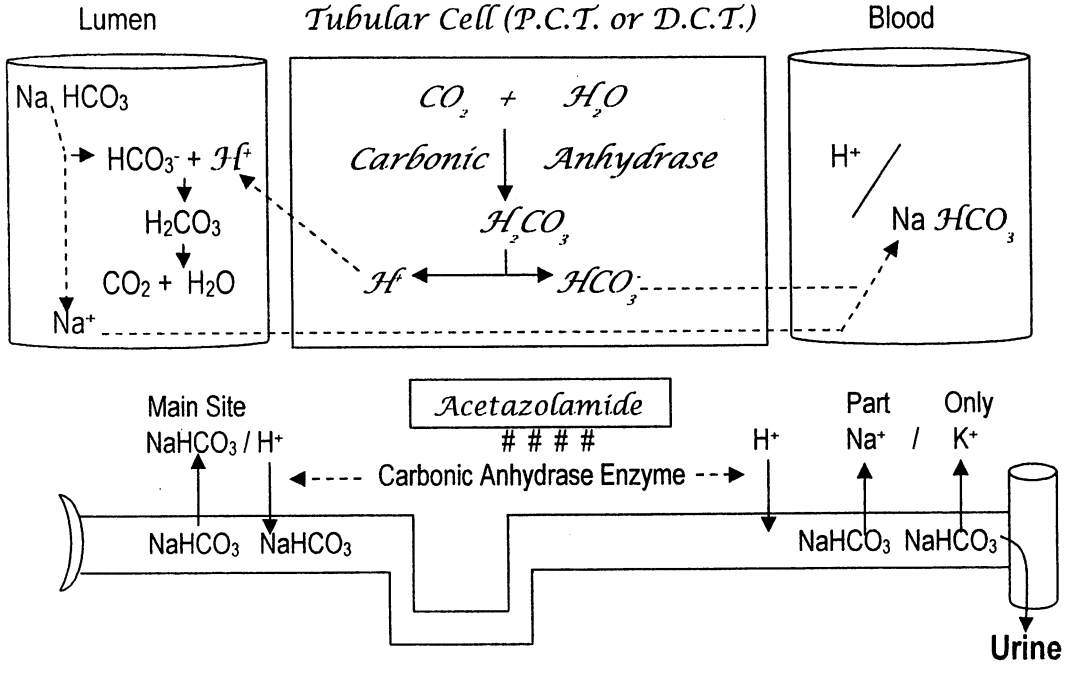
7- Tienilic Acid (Ticrynafen): } Uricosuric effect



	Thiazide Diuretics	Loop Diuretics
1- Example:	Hydrochlorothiazide	Frusemide
2- Main Site of Action:	Cortical Diluting Segment	Medullary Part of Thick Ascending Loop of Henle
3- C.C.M.S.:	No effect	Interfere
4- Carbonic Anhydrase:	Mild ↓ (Sulfonamide)	Mild ↓ (Sulfonamide)
5- Mg^{2+} in urine:	↑	↑
6- Ca^{2+} in urine:	↓	↑
7- R.B.F.:	↓	↑
8- Efficacy:	Moderate	High
9- Arterial V.D.:	Direct V.D. (↑ K^+-Channel)	No Direct V.D.
10- Uses:	1- Mild & Moderate a- C.H.F. b- Hypertension 2- Hypercal***curia***	1- Emergency & Severe: a- Heart Failure b- Hypertension 2- Hypercal***cemia*** 3- Renal Failure
11- Adverse Effects:	1- Hypokalemia 2- Hyponatremia 3- Hypochloremic Alkalosis 4- Hypomagnesemia 5- Hypovolemia 6- Hyp***er***calcemia 7- Hyperglycemia 8- Hyperlipidemia 9- Hyperuricemia 10- Hypersensitivity 11- G.I.T. 12- Fetotoxic	1- Hypokalemia 2- Hyponatremia 3- Hypochloremic Alkalosis 4- Hypomagnesemia 5- Hypovolemia 6- Hyp***o***calcemia 7- Hyperglycemia 8- Hyperlipidemia 9- Hyperuricemia 10- Hypersensitivity 11- G.I.T. 12- Fetotoxic 13- Deafness 14- Dehydration

III- Carbonic Anhydrase Enzyme Inhibitors

Acetazolamide (Diamox, Cidamex)



* Pharmacodynamics:

- Sulfonamide derivative.
- Reversible Non-competitive inhibitor of Carbonic Anhydrase Enzyme (CAE).

1- Kidney: Weak Self-Limiting Diuretic

1- Acetazolamide ↓ $NaHCO_3$ reabsorption in exchange for H^+ *Mainly* in P.C.T. and also in Late part of D.C.T.

2- Excess $NaHCO_3$ will reach the late part of D.C.T. where *Part* of Na^+ is reabsorbed in exchange for K^+ *ONLY*.

3- The remaining $NaHCO_3$ will be excreted in urine with its iso-osmotic water.

4- The urine will contain:

a- Excess water → Weak diuretic effect (Low Efficacy)

b- Excess Na^+ → Natriuretic effect → Hyponatremia

c- Excess HCO_3 → Alkaline urine → Acidosis (Characteristic).

d- Excess K^+ → Kaluretic effect → Hypokalemia

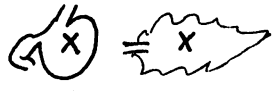
e- ↓ NH_4^+ in urine (No available H^+) → *Dangerous in Hepatic patients.*

5- ↓ HCO_3 reabsorption; while Cl^- reabsorption is *NOT* affected → Relative ***Hyperchloremic Acidosis*** → ↑ Availability of H^+ for exchange with urinary Na^+ → ↓ Diuretic effect → Self-Limiting Diuretic.

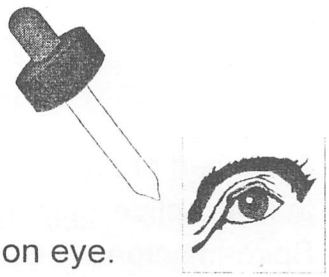
2- Eye: ↓ Synthesis of Aqueous Humor formation → ↓ I.O.P.

3- C.N.S. ↓ either due to ↑ CO_2 or Acidosis → Anti-Epileptic effect.

4- Therapeutic Doses → ***NO*** effect on Gastric or Pancreatic secretions.



* *Therapeutic Uses of Acetazolamide:*



250 – 500 mg / day Orally or I.V.

1- As a diuretic *BUT* → Weak & Self-limiting.
2- Glaucoma: Orally (Open angle) & I.V. (Closed angle) N.B.)
   a- Dichlorphenamide *(Oratrol, 50 mg Orally)*: More specific on eye.
   b- Dorzolamide *(Truspot, 2%)* Eye drops in Glaucoma.
3- Petit mal epilepsy (Absence seizures) when other drugs fail.
4- Alkalinizer of urine e.g. to dissolve uric acid crystals.

* *Adverse Effects of Acetazolamide:*

1- Weak & Self limiting.
2- Hypokalemia (See before).
3- Hyperchloremic Acidosis → Self-limiting.
4- Alkalinizes the urine → Phosphaturia → Crystaluria & calculi.
5- Aggravate Hepatic insufficiency due to inability to excrete ammonia.
6- C.N.S. inhibition → Sedation & paresthesia.
7- Allergy & Cross-allergy with other sulfonamides.

IV- Potassium Retaining (Sparing or Conserving) Diuretics

1- They ↓ ***Na^+/K^+ exchange*** in the ***late part of D.C.T.***
2- Na^+ will be retained in urine with its iso-osmotic water → ***Weak (Low Efficacy) Diuresis.***
3- K^+ will be retained in Blood → ***Hyperkalemia***:
   a- Do *NOT* add KCl supplement.
   b- Avoid in Renal insufficiency.
   c- Not used with ACE.I, AT_1-blockers, β-Blockers & NSAID → ↑ Hyperkalemia.

* *Classification:*

A) Aldosterone Antagonists:

Effective *ONLY* in presence of mineralocorticoids e.g. Aldosterone.

1- *Competition with Aldosterone*: Spironolactone.
2- *Inhibit Synthesis of Aldosterone*:
   a- Metopirone (Metyrapone) → ↓ 11-β-Hydroxylase enzyme *(see Hormones).*
   b- Angiotensin Converting Enzyme Inhibitors (Captopril) & AT_1-receptor blockers (Losartan) → ↓ Angiotensin II *(See CVS).*

B) Non-Aldosterone Antagonists: Triamterene & Amiloride

1- Block directly Na^+-channels in D.C.T.
2- Effective even in absence of Aldosterone e.g. after Adrenolectomy.

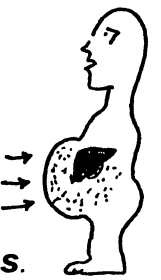
A- Aldosterone Antagonists

Spironolactone (Aldactone)

1- Absorbed orally.
2- In liver Active Spironolactone → Active Canrenone.
3- Spironolactone & Canrenone *Compete* with Aldosterone for its specific receptors in the late part of D.C.T. → ↓ Na^+/ K^+ *Mainly*, also ↓ some Na^+/H^+ Exchange →
   a- Retention of Na^+ in urine with its iso-osmotic water → Weak (Low efficacy) diuresis.
   b- Retention of K^+ in blood → Hyperkalemia.
   c- Retention of some H^+ in blood → Acidosis
4- Spironolactone ↑ Ca^{2+} excretion in urine.

Urine	Blood
↑ Na & ↑ Ca	↑ K & ↑ H

* Therapeutic Uses of Spironolactone:



Spironolactone *(Aldactone) 25 mg Oral tablets → 1 - 4 tablets / day*

1- **HYPERALDOSTERONISM** → Edema & Hypertension:
   a- Primary: Tumor of Adrenal Medulla *(Conn's Syndrome)*.
   b- Secondary to C.H.F., Nephrotic Syndrome & ***Liver Cirrhosis*** → ***Ascites***.
2- Refractory Edema e.g. CHF, Nephrotic Syndrome & ***Liver Cirrhosis*** → ***Ascites***.
3- Essential Hypertension: Spironolactone ↓ Bl.p. by its diuretic effect (*No V.D.*).
4- In Combination with Thiazide or Loop diuretics:
   a- Synergize their diuretic effect.
   b- Correct their hypokalemia.

- Spironolactone + Hydrochlorothiazide → Aldactazide.
- Spironolactone + Frusemide → Lasilactone, Fructone.

5- To substitute Thiazide & Loop diuretics when they are contraindicated e.g. Hypokalemia, hyperglycemia, hyperlipidemia, hyperuricemia & hypersensitivity.

* Adverse Effects of Spironolactone:

1- HypERkalemia:
   a- *NOT* Add KCl supplement b- *NOT* Renal insufficiency.
   c- *NOT* with ACE.I, AT_1-blockers, β-Blockers or NSAID.
2- Weak diuretic (Low efficacy) & Slow onset (2-3 days).
3- Antagonizes the action of Digitalis (Heart Failure) & Carbenoxolone (Peptic ulcer).
4- C.N.S.: Confusion, Drowsiness & Headache.
5- Hormones:
   a- Males → Gynecomastia & Impotence.
   b- Females → Menstrual disturbances & Hirsutism.
6- G.I.T. disturbances.
7- Allergy.

B) Non-Aldosterone Antagonists

- Triamterene *(Dyrenium)* 100 mg bid PO.
- Amiloride *(Midamor)* 5 mg od PO.

1- *Potassium retaining* diuretics.
2- Non-Aldosterone antagonist. They *block directly the Na^+-Channel at D.C.T.* →
   a- ↓ Na^+/K^+ Exchange → Weak diuresis (Low efficacy) + Hyperkalemia
   b- ↓ Excretion of H^+ & Ca^{2+} in urine → Acidosis + Hypercalcemia.
3- Mild *uricosuric* effect.
3- Usually *used* in combination with Thiazide & loop diuretics:
   a- Synergism.
   b- Correct hypokalemia.
   c- Correct hyperuricemia.

- Triamterene + Hydrochlorothiazide → Dyazide, Thiamterene.
- ***Amiloride 5 mg+ Hydrochlorothiazide 50 mg→ Moduretic***

4- *Adverse effect*: Hyperkalemia, GIT disturbances + Allergy
5- *Contraindication*: Renal insufficiency.
6- *Drug interactions*:
   a- ACE.I., AT_1-blockers, β-Blockers & NSAID → ↑ Hyperkalemia.
   b- Triamterene + Indomethacin → Renal failure

V- Osmotic Diuretics

1- Osmotic.
2- Small M.W. → Freely filterable through glomeruli.
3- Minimal or no renal reabsorption.
4- ↓ Water reabsorption from PCT, Descending Loop of Henle & Collecting tubules.
5- Not metabolized, Not active (Inert) & Non-toxic.

A) Mannitol:

1- 100 ml 25% solution I.V.
2- Not reabsorbed from the renal tubules → Zero renal threshold.
3- Used to ↓ I.O.P., ↓ Intra-Cranial Pressure & Acute renal failure.
4- Causes Transient expansion of extracellular fluid volume → Pulmonary edema.
5- If taken orally → Not absorbed → Diarrhea.

B) Urea: 50% Renal reabsorption. 30% solution I.V. → ↓ I.C.P.

C) Glucose: High renal threshold 180 mg%. 50 ml 50% solution I.V.

D) Glycerin & Isosorbide: Orally → ↓ I.O.P.

VI- Methyl-xanthines

1- Examples: Theophylline (Aminophylline) > Theobromine > Caffeine
2- Extra-renal: ↑ C.O.P. + Renal V.D. → ↑ R.B.F. & ↑ G.F.R.
3- Renal → ↓ NaCl from the nephron.
4- Aminophylline I.V. in Acute pulmonary edema.

VII- Acidifying Diuretics

Ammonium Chloride (NH_4Cl)

1- *Weak self-limiting* diuretic.
2- *Causes* Hyperchloremic Acidosis & Acidification of urine.
3- *Therapeutic Uses*:
   a- Correct Alkalosis.
   b- Hypocalcemia & Tetany ($NH_4Cl \rightarrow$ Acidosis $\rightarrow \uparrow$ Solubility constant $\rightarrow \uparrow Ca^{2+}$ in Blood).
   c- Acidify the urine:
      - Help excretion of weak base drugs e.g. Ephedrine & amphetamine.
      - Potentiate urinary disinfectants e.g. Methenamine.
   d- Nauseant Expectorant.
4- *Contraindicated* in liver & kidney diseases.

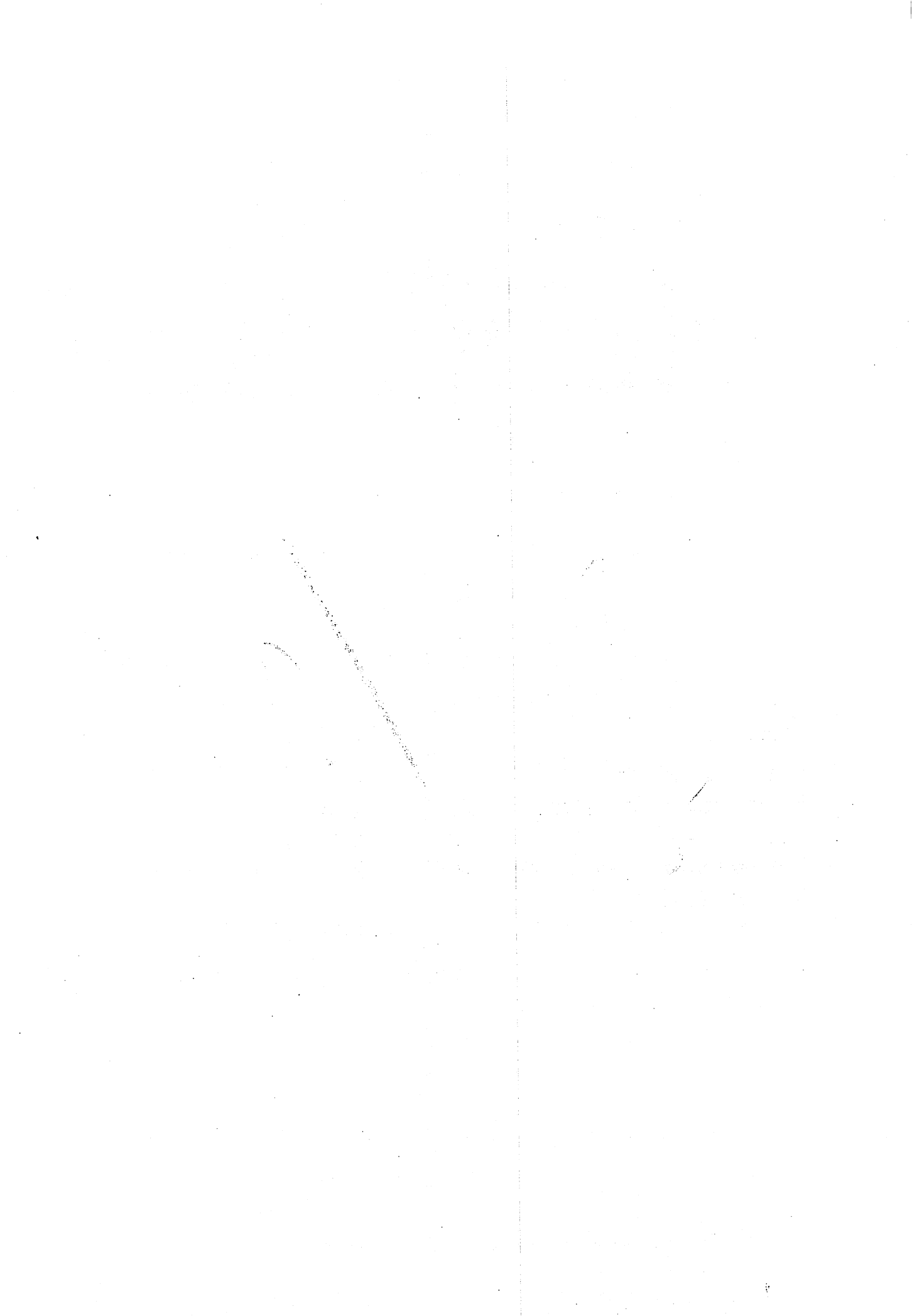
N.B.) Acidifiers of urine:
1- **A**mmonium chloride, **A**scorbic acid (Vit C), **M**ethionine & **M**andelic acid.
2- Uses (See Ammonium chloride).

NB) Alkalinizers of Urine:
1- Na or K **A**cetate, **B**icarbonate or **C**itrate.
2- Therapeutic Uses:
   a- Treat acidosis.
   b- Alkaline expectorant.
   c- Alkalinize the urine:
      - Help excretion of weak acid drugs e.g. Aspirin & Phenobarbitone.
      - Dissolve & help excretion of uric acid $\rightarrow$ Treat gout.
      - Potentiate sulfonamides & prevent Crystaluria.
      - Decreases dysuria (Burning micturition) & $\downarrow$ Growth of E.coli $\rightarrow$ Treat U.T.I.

N.B.) Anti-Diuretics:
1- A.D.H. $\rightarrow$ Treat Hpothalamo-pituitary diabetes insipidus.
2- $\uparrow$ A.D.H. Release: Nicotine, Morphine, Barbiturates, Yohimbine & Ether.
3- Thiazide diuretics *ONLY* in Nephrogenic Diabetes insipidus.
4- Chlorpropamide (Oral hypoglycemic) & Carbamazepine (Anti-epileptic) $\rightarrow$ ADH like.
5- Renal V.C. e.g. Adrenaline, Noradrenaline & Dopamine L.D.
6- Na^+ & Water retention e.g. Mineralocorticoids & Phenylbutazone.
7- Serotonin.

N.B.) ADH - Antagonists:
1- Useful in treatment of Syndrome of Inappropriate ADH Secretion (S.I.ADH) $\rightarrow$ Chronic hyponatremia.
2- Examples:
   a- Lithium carbonate (Mood stabilizer & Anti-manic).
   b- Demeclocycline (Tetracycline Antibiotic).
   c- Methoxyflurane (General anesthesia).

C. V. S.



Angina Pectoris (الذبحة الصدرية)

- Chest pain due to transient myocardial ischemia.
- Cardiac ischemia is due to imbalance between:
  a- Cardiac work = O_2 needs of myocardium and
  b- Coronary flow = O_2 supply

* *Types of Angina Pectoris:*

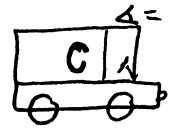
1- Angina of Effort (Exertional, Stable, Classic):

a- Most common type. Occurs on exertion.
b- Due to *coronary* ***atherosclerosis*** → Coronary lumen is narrowed & fixed.
c- Treatment by ***↓ Cardiac work***.

2- Variant (Prinzmetal, Vaso-spastic) Angina:

a- Occurs at rest, usually accompanied by arrhythmia.
b- Due to *reversible coronary* ***V.C.*** = Supersensitive coronary.
Diagnosed by ergometrine.
c- Treatment by *Coronary* ***V.D.***

3- Unstable Angina (Pre-infarction, Crescendo):



a- Progressive worsening → Occurs on mild exertion then on rest.
b- Progressive ***occlusion*** of coronary artery on top of atherosclerosis.
c- Treatment: *Hospitalization + Coronary V.D. + ↓ Cardiac work + Anti-thrombotics.*

* *Drug Treatment of Angina:*

A) Anti-Anginal Drugs:

1- Nitrites & Nitrates ⟶ Both → Coronary V.D. + ↓ Cardiac work.
2- Calcium Channel Blockers (CCB) → Both → Coronary V.D. + ↓ Cardiac work.
3- β-Blockers ⟶ ↓ Cardiac work.
4- Other drugs:
   a- Nicorandil → Nitrodilator (NO release) + K^+-channel opener → V.D.
   b- Trimetazidine *(Vastarel)* → Anti-ischemic Cyto-protective drug.

B) Adjuvant Drugs:

1- Anti-Platelet:
   a- Prevent conversion of Stable Angina → Unstable angina
   b- Examples: Aspirin, Dipyridamol & Ticlopidine (see Blood).
2- Drug treatment of Risk & Precipitating factors e.g. Anti-anxiety, Antihypertensive, Anti-hyperlipidemic, Anti-diabetic, etc.

Drug Group	Decrease Cardiac Work			Coronary VD
	Arterial VD ↓ After load	Veno-VD ↓ Preload	↓ Heart -ve Ino & -ve Chrono	
1- Nitrites & Nitrates		+ + +		+ + +
2- C. C. B.	+ + +		+++ (Verapamil)	+ + +
3- β-Blockers			+ + +	

1- Nitrites & Nitrates

* Classification:

A) Nitrites:

1- Organic Nitrites e.g. **Amyl Nitrite** Inhalation.
2- Inorganic Nitrite e.g. **Na^+ Nitrite** I.V.
3- *They produce Met-Hb → Useful in Cyanide poisoning But harmful in Angina.*

B) Organic Nitrates: *Inorganic Nitrates are Inactive*

1- Isosorbid Mononitrate.
2- Isosorbid Dinitrate.
3- Glyceryl Trinitrate (GTN, Nitroglycerin).
4- Erythrityl Tetranitrate
5- Pentaerythritol Tetranitrate.
6- Mannitol Hexanitrate.

* Pharmacokinetics:

1- Absorbed from Buccal & Intestinal mucosa, and skin.
2- Extensive hepatic first pass metabolism (90 %) → 10 % Oral bioavailability.
3- Excreted as Glucuronide conjugates.

* Pharmacodynamics:

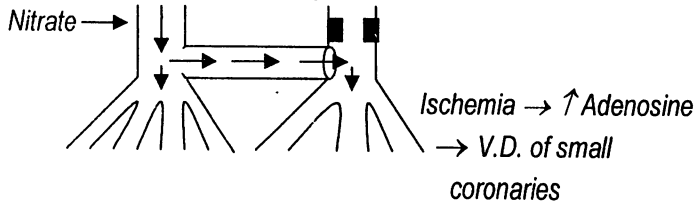
In the body Nitrites & Nitrates are *denitrated* by Glutathione transferase enzyme (consuming S-H group) → Release of Nitric Oxide (NO) → ↑ Soluble Guanylate Cyclase enzyme → ↑ cGMP:

a- Dephosphorylation of Myosin light chain → Smooth muscle relaxation → V.D.
b- ↓ Platelet aggregation.

V.D. of ***Normal*** , Mainly ***Big*** , Especially ***Veins***

Good

1- MAINLY Veno-Dilatation → ↓ VR → ↓ EDV →
a- ↓ Pre-Load MAINLY.
b- ↓ Contractility → ↓ Pressure on Subendocardial coronaries.
c- ↓ C.O.P. → ↓ Systolic Bl.p. MAILNY.
2- Some Arterial V.D. → ↓ TPR →
a- After-load.
b- ↓ Diastolic Bl.p.
3- V.D. on Normal Big Epicardial Coronaries →
Redistribution of coronary flow to ischemic area



Bad

1- Meningeal V.D. → Headache.
2- Retinal V.D. → ↑ I.O.P.
3- Cutaneous V.D. → Flush.
4- Peripheral V.D. → Postural hypotension & syncope
5- ↓ Bl.p. → Reflex ↑ Sympathetic:
a- Tachycardia
b- Short Diastolic coronary perfusion.
c- Add β-Blocker or Verapamil (CCB).
6- Tolerance, Cross-tolerance & Dependence due to depletion of S-H:
a- Nitrate free intervals
b- Alternate every 2 weeks.
7- Met-Hb.
8- Hypersensitivity.
9- Formation of Nitrosamines.

* Pharmacological Actions of Nitrates:

1- Blood Vessels → V.D. of Normal, Mainly Big & Especially Veins.

a- **POWEFUL Veno-V.D. → ↓ V.R. → ↓ E.D.V. → ↓ Pre-Load.**

b- Some Arterio-V.D. → ↓ T.P.R. → ↓ After-load.

c- V.D. of Big Epicardial Normal Coronaries → Redistribution to ischemic area.

d- Meningeal V.D. → Headache → Good sign. If absent → Tolerance or expired tablets.

e- Retinal V.D. → ↑ I.O.P.

f- Cutaneous V.D. → Flush of face & chest (Blush area) → Nitroid reaction.

g- Pulmonary V.D. & ↓ V.R. → ↓ Pulmonary pressure.

2- Heart:

a- Decrease Cardiac work (↓ Preload > ↓ Afterload) & ↓ Oxygen consumption.

b- POWERFUL Veno-Dilator → ↓ V.R. → ↓ E.D.V. →

- **↓ Pre-load**
- **↓ Contractility → ↓ Pressure on Sub-endocardial coronaries.**

c- Some Arterio-V.D. → ↓ T.P.R. → ↓ Afterload.

d- Hypotension → Reflex ↑ Sympathetic → ↑ Contractility &Tachycardia → Shorten Diastolic Coronary Perfusion Time # by β-Blockers or Verapamil (CCB).

3- Hypotension: ↓ S.Bl.p. > D.Bl.p.

4- Spasmolytic on smooth muscles of Bronchial, biliary, GIT, UB & Uterus.

5- Reflex ↑ R.C.: ↑ Chemo- & Baro-receptors

* Therapeutic Uses of Nitrites & Nitrates:

1- All Types of Angina Pectoris:

★ Mechanism:

1- Angina of Effort → ↓ Cardiac work (↓ Pre > After-load) & ↓ O_2 consumption.

2- Variant Angina → Coronary V.D.

3- Unstable angina → ↓ Cardiac work + ↓ O_2 consumption + Coronary V.D.

★ Use:

1- In **Acute Attack** (Present anginal pain) & **Immediate Prophylaxis** (Before exertion or stress) → *Use Rapidly Acting Preparations* → **Nitroglycerin or Isosorbid Dinitrate *(Sublingual or Buccal spray)***.

Precautions:

a- Patient must sit to avoid postural hypotension & syncope.

b- Get rid of excess drug by either spitting or swallowing.

2- In **Long Term Prophylaxis** → *Use Long Acting Preparations* → Slow release Oral preparations (Large dose to overcome Hepatic First Pass Effect) or Transdermal Patch or ointment.

Precautions:

a- 8-10 Hours nitrate-free period or alternate every 2 weeks to avoid tolerance.

b- Never Stop nitrate therapy *Suddenly* → Rebound ischemia & infarction.

c- Do *NOT* take double dose. If a dose is missed → wait for the next dose.

d- Do *Not* use after expiry date → No effect.

e- Not combined with ***Sildenafil*** *(Viagra)* → *Severe Hypotension → May be Fatal*

3- Nitroglycerin I.V. Infusion in:

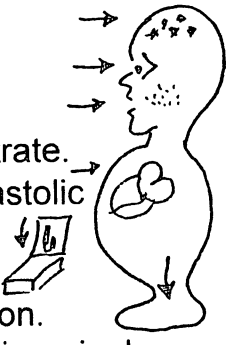
a- Acute myocardial infarction (A.M.I.), Acute Pulmonary Edema (Acute Left Ventricular Failure) & Refractory H.F. → ↓ Preload & ↓ Pulmonary congestion.

b- During Coronary bypass surgery.

c- Controlled hypotension during Non-cardiac operations.

4- Biliary Colic. **5- Bronchial Asthma**

6- Contraction Ring of uterus. **7- Cyanide poisoning**: Use Nitrites.



* Adverse Effects of Nitrites & Nitrates:

1- Headache, Flush & ↑ I.O.P.

2- Postural hypotension & Syncope. Sit while taking rapidly acting nitrate.

3- Hypotension → Reflex ↑ Sympathetic → Tachycardia → Short Diastolic Coronary perfusion # by β-Blockers or Verapamil (CCB).

4- Tolerance & cross-tolerance between nitrites & nitrates:
   a- Due to depletion of S-H group required for denitration & activation.
   b- Avoid by daily 8-10 hours nitrate free or alternate with other Anti-anginals every 2 weeks.

5- Coronary Dependence after prolonged exposure to nitrates.
   Sudden stop of Nitrates → Rebound coronary V.C. → Ischemia & Infarction.

6- Hypersensitivity reactions.

7- Met-Hb especially by Nitrites > Nitrates.

8- Nitrites & Nitrates + Amino group → Nitrosamines → Carcinogenic.

* Preparations & Doses of Nitrates:

1- Glyceryl Trinitrate (Nitroglycerin, GTN):

a- Sublingual *(Angised):*

1- Dose: 0.5 mg/5 min; Max 3 doses. Onset: 1-3 min. Duration: 10-30 min.

2- Avoids extensive hepatic first pass metabolism.

3- Effective in ***Acute attacks*** (may be repeated every 5 min till pain disappears or maximum 3 doses) & ***Immediate Prophylaxis*** (taken 5 minutes before effort).

4- If side effects appear; either → Spit or Swallow the pellet.

b- Buccal Spray: 0.4 mg/Metered dose. Duration: 1.5 hours.

c- Oral Sustained Release (SR) Preparations *(Nitromack & Nitroguard) :*

1- Dose: 6.25-12.5 mg/2-4 times/day. Onset: 1 hour. Duration: 4-8 hours.

2- Low (< 10%) oral Bioavailability. The Dinitrate metabolite is also active.

3- Useful in long term Prophylaxis.

d- Transdermal Delivery System (TDDS): For Nocturnal Prophylaxis.
- Ointment *(Nitroguard)* 2%. 1-1.5 inch/4 hours. Duration: 3-6 hours.
- Transdermal patches *(Nitroderm TTS)* : 25 mg/day. Duration: 8-12 hs.

e- IV Infusion *(Nitrostat, Tridil):* 10-20 ug / min in Emergency AMI or Acute Pulmonary Edema.

2- Isosorbid Dinitrate:

a- Sublingual *(Dinitra, Isordil) :*

1- Dose: 5 mg. Onset: 2-5 min. Duration: Up to 1 hour.
2- Useful in Acute Attacks & Immediate Prophylaxis (See Nitroglycerin).

b- Buccal Spray: Dose 1.25 mg/Metered Dose. Duration: 1.5 hours.

c- Chewable tablet.

d- Oral *(Dinitra, Isordil, Coronit, Effox, Cardiket, Isomack & Cardioguard):*

1- Tablets: 10 - 40 mg / 4-6 hours Duration: 4 - 6 hours.
2- S.R. Capsules: 20 - 40 mg / 12 hours Duration: 6 – 12 hours
3- Useful for Long Term Prophylaxis (See Nitroglycerin).

3- Isosorbid Mononitrate *(Monocard, Corangin):*

1- Tablets: 20 mg/12 hours Orally for Long Term Prophylaxis. Duration: 6-10 hs.
2- S.R. Capsules 60-120 mg once daily. Duration: 24 hours.

4- Erythrityl Tetranitrate: 15 mg Oral & SL.

5- Pentaerythritol Tetranitrate *(Cortranquil)*: 15 mg Oral Only.

6- Mannitol Hexanitrate: 30 mg Oral & SL.

NB) Other Anti-Anginal Drugs:

1- Nicorandil:

1- Oral V.D. → ↓ Preload & Afterload:
   a- Nitrate-like → Release NO = Nitrodilator.
   b- Opens ATP-dependent K^+-Channel.
2- V.D. of Normal Large Epicardial coronaries.
3- Useful in Angina & Heart failure.
4- No tolerance.
5- Headache.

2- Molsidomine: An Oral Veno-dilator similar to Nitrates; BUT NO Reflex ↑ H.R.

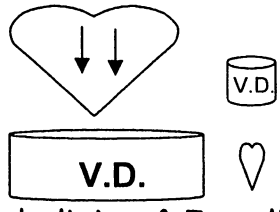
3- Trimetazidine *(Vastarel, 20 mg):*

1- Anti-Ischemic & Cytoprotective:
   a- Improve cell respiration → ↓ lactate production → ↓ Intracellular acidosis
   b- ↓ Intracellular Ca^{2+} overload.
   c- ↓ Free radical production.
2- Used orally in Effort Angina.

Calcium Channel Blockers (CCB)

* Classification:

1- Phenylalkylamines: **Verapamil** → ↓ *Heart* > V.D.
2- Benzothiazepines: **Diltiazem** → ↓ Heart > V.D.
3- Dihydropyridines (D.H.P.) → *V.D.* > ↓ Heart:
   a- Long Acting: Amlodipine.
   b- Intermediate Acting: **Nifedipine**, Nitrendipine, Felodipine & Isradipine.
   c- Short Acting: Nicardipine & Nimodipine.



* Pharmacokinetics:

	Verapamil	Diltiazem	Nifedipine
1- Oral Absorption :	Well	Well	Well
2- Oral bioavailability:	Low (20 %)	Moderate (40 %)	High (60 %)
3- First pass met. :	High	Moderate	Little
4- Binding to p. ptns:	High (90 %)	High (80 %)	High (90 %)
5- Fate :	- Hepatic metabolism - Renal & biliary excretion	- Hepatic metabolism - Renal & biliary excretion	- Hepatic metabolism - Renal & biliary excretion
6- t ½ :	4 hours	4 hours	2 hours

* Pharmacodynamics:

I- Mechanism of Action:

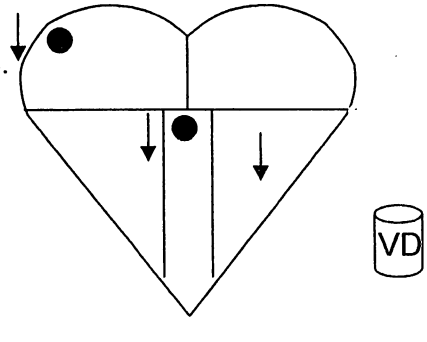
1- They bind to α-subunit of the channel → Block **Voltage-dependent L-type** calcium channels present in Heart, Blood vessels and Smooth muscles.
   Types of calcium channels are L, N, T & P.
2- They ↓ Ca^{2+} influx into:
   a- ***Cardiac*** muscle → Cardiac inhibition (Especially ***Verapamil & Diltiazem***).
   b- ***Blood vessels*** → Arteriolar VD (Especially ***Nifedipine***).
   c- ***Smooth muscles***→ Relaxation e.g. Bronchial, Biliary, GIT, Urinary & Uterus.

II- Pharmacological Actions:

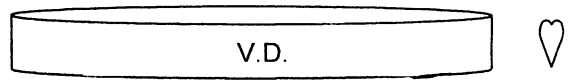
A) C. V. S.: {Verapamil ↓ **Heart** > VD while Nifedipine **VD** > ↓ Heart}

1- Verapamil & Diltiazem (↓ *Heart* > VD):

1- *POWERFUL **CARDIAC DEPRESSANT***:
   a- -ve Chronotropic Effect = ↓ SAN = Bradycardia:
      - Long Diastolic Perfusion Time for the coronaries.
      - Antagonizes Tachycardia induced by Nitrates.
   b- -ve Inotropic Effect = ↓ Contractility:
      - ↓ Cardiac work & ↓ Oxygen consumption.
      - Contraindicated in Heart Failure.
   c- -ve Dromotropic effect = ↓ AV Conduction:
      - Contraindicated in Heart Block.
      - NOT Combined with β-Blockers or Digitalis.
   d- ↓ Automaticity → ↓ Ectopic Focus Formation → Class IV Anti-Arrhythmic.
2- *Less* peripheral **V.D.** than Nifedipine *BUT POTENT* Coronary V.D.
3- *Less* **Hypotension** than Nifedipine.



2- Nifedipine (*V.D.* > ↓ Heart):



1- *POWERFUL **V.D.*** (ARTERIAL > Vein in contrast to Nitrates):
- a- Coronary VD: VD of *SMALL* coronaries on the non-ischemic area may steal the blood from the atherosclerosed area → **Coronary Steal Phenomenon**.
- b- Potent Arterio-Dilator → ↓ TPR → ↓ AFTER-LOAD. } ↓ Cardiac Work &
- c- Weak Veno-dilator ——→ Less ↓ VR → ↓ Preload. } ↓ O_2 - Consumption.
- d- Hypotension → Reflex ↑ Sympathetic → Tachycardia → Short Diastolic Filling. Better ADD β-Blocker. Better not used ALONE with Nitrates.

2- Very Weak Myocardial Depressant:
- a- Does NOT ↓ SAN. It even causes TACHYCARDIA.
- b- Does NOT ↓ AVN. Allowed in Heart Block.
- c- Minimal -ve Inotropic → COP is maintained or may increase → Allowed in HF.
- d- It is NOT an Anti-arrhythmic.

B) Other Actions of CCB:

a- *↓ Platelet aggregation*.
b- *Smooth muscle relaxation* e.g. Bronchial, Biliary, GIT, Urinary & Uterine.
c- *Skeletal muscle*: ***No*** effect, they depend on intracellular calcium pool.
d- *Endocrine*: Verapamil ↓ insulin release.

* Therapeutic Uses of CCB:

1- ***ALL Types Of Angina*** (↓ Cardiac Work & Coronary VD):

***Mechanisms of CCB in Angina**:

1- Coronary VD → Treat ***Variant Angina.*** } Treat ***Unstable Angina.***
2- ↓ Cardiac Work & ↓ O_2 consumption → Treat ***Effort Angina*** }
- a- **Powerful ARTERIOLAR DILATOR → ↓ TPR → ↓ AFTER-LOAD.**
- b- Mild Veno-Dilator → Mild ↓ VR → Mild ↓ Preload.
- c- -ve Inotropic effect.

3- Preserve energy stores.
4- ↓ Platelet aggregation.

***Uses of CCB in Angina**:

1- *In Acute Attack of Angina*: Sublingual Nifedipine may be useful
2- *In Prophylaxis of Angina*:

a- Verapamil & Diltiazem:
- Indicated specially in Angina + Cardiac arrhythmia.
- Verapamil + Nitrates → Good combination
  - * Nitrates → Coronary VD + Venodil + ↓ Preload + ↑ HR + ↓ Diastolic time
  - * Verapamil → Coronary VD + Arteriodil + ↓ Afterload + ↓ HR + ↑ Diastolic time.
- Verapamil + β-Blocker → Severe Heart Block → Bad combination.

b- Nifedipine:
- Indicated specially if angina + Hypertension or Bronchial asthma.
- Nifedipine (↑ HR) + β-Blockers (↓ HR) → Good combination.
- Nifedipine (VD & ↑ HR) + Nitrates (VD & ↑ HR) → Severe ↓ Bl.p. & ↑ HR

2- *Acute myocardial **Infarction*** → Cardio-protective.
3- ***Preservation*** of ischemic myocardium during open heart surgery.

4- Cardiac ***Arrhythmias*** especially **Verapamil**:
   a- IV verapamil is the drug of choice in re-entrant PAT.
   b- ↓ HR in atrial flutter & fibrillation.
5- Hypertrophic ***Obstructive*** *Cardiomyopathy* with subaortic stenosis: Verapamil & Diltiazem → -ve ino + -ve Chrono → More filling & arterial VD → More emptying
6- ***Hypertension*** especially **Nifedipine** → Arterial VD → ↓ TPR → ↓ Bl.p.
7- ***P.V.D.*** especially D.H.P. group.
8- ***Cerebral*** *spasm* in response to subarachnoid hemorrhage: **Nimodipine**.
9- ***Migraine*** *headache*: **Nimodipine & Flunarizine.**
10- *Acute* ***bronchial asthma*** → Spasmolytic effect especially D.H.P. group.
11- *Premature* ***labour*** & ***Toxemia*** *of pregnancy*.
12- Acute & Chronic ***Renal Failure*** → They ↑ Renal blood flow & ↑ Renal function.

** Adverse Effects of CCB:*

1- Headache & flush.
2- Heart:
   a- **Verapamil & Diltiazem** →
      - -ve Inotropic → Heart failure.
      - -ve Chronotropic → Bradycardia.
      - -ve Dromotropic → Heart Block.

   } NOT combined with β-Blockers.

   b- Nifedipine → Tachycardia & may aggravate angina by its steel phenomena.
4- Hypotension.
5- Constipation specially Verapamil.
6- Reversible liver impairment.
7- Ankle edema specially Nifedipine
8- *Drug Interactions*:
   a- Verapamil ↓ Renal excretion of Digoxin.
   b- Verapamil + β-Blocker → Severe Cardiac depression.
   c- Nifedipine + Nitrates → Severe Hypotension & Tachycardia.

Calcium Channel Blockers (CCB)

A) *Phenylalkylamines*: **Verapamil** *(Isoptin)*: 80-160 mg tds or SR 240 mg od Orally.

B) *Benzothiazepines*: **Diltiazem** *(Altiazem, Tildiem)*: 60-120 mg tds or SR bid Orally

C) Dihydropyridine Group:

Useful in Angina, Hypertension & P.V.D. e.g. Raynaud's disease

1- **Nifedipine** *(Epilat, Nifepin, Dilcor)*: 10 - 40 mg tds or SR bid Orally
2- **Amlodipine** (Norvasc): Longest $t_{1/2}$ (30 - 50 hs), 5-10 mg ONCE/day Orally.
3- **Nicardipine** (Micard): 20 - 50 mg bid
4- **Nimodipine** (Nimotop): 30 mg bid
   a- Useful in Cerebral vascular accidents e.g. Subarachnoid hemorrhage.
   b- May be useful in Migraine headache.
5- **Isradipine** (Lomir): 2-5 – 5 mg bid
6- **Lacidipine** (Lacipil): 2 – 4 mg bid
7- **Felodipine** (Plendil).

C) Other CCB:

1- **Flunarizine** (Sibelium):

a- Prophylaxis of Migraine headache.
b- Peripheral vascular diseases.

2- **Indapamide** (Natrilex):

a- Related to Thiazide Diuretics.
b- Used in Sub-diuretic dose in treatment of Hypertension.
c- Advantages:
- Minimal effect on Electrolytes, Glucose, Uric acid & Lipid metabolism.
- Long Acting → Used 2.5 mg ONCE/Day.
- Depends on Biliary excretion, so allowed in patients with Renal impairment.

3- **Bepridil** → ↓ Heart > V.D.
4- **Amiodarone** (Cordarone) → Anti-Anginal + Class III Anti-arrhythmic.

III- β-Blockers

1- *All β-Blockers* (selective or non-selective) are effective in angina pectoris:
a- Better use β-Blockers with***out*** I.S.A.
b- ***Non***-selective: ***Propranolol & Nadolol.***
c- ***Selective*** β_1-Blockers e.g. ***Atenolol, Metoprolol & Bisoprolol.***
d- ***Vaso-dilator*** β-Blockers e.g. ***Carvedilol***

2- They do *NOT* produce coronary V.D. Non-selective β-Blockers may cause V.C. of normal coronaries → Shift & Redistribution of coronary flow to ischemic area.

3- *Desirable Effects* → ↓ Cardiac work & ↓ O_2-consumption:
a- ↓ H.R. → Resting HR 50-60 b/min or Max HR 100-120 b/min:
- ↑ Diastolic coronary perfusion time.
- Prevent tachycardia induced by Anxiety & Exercise.
- Prevent tachycardia induced by Nitrates & Nifedipine.

b- ↓ Contractility.
c- Long use → Anti-hypertensive → ↓ After-load.

4- *Undesirable* effects: Bradycardia →
a- Long diastole → ↑ E.D.V. → ↑ Preload.
b- Long Systole → ↑ Ejection time.
} - ↑ O_2-needs → Offset desirable effects
- Can be balanced by Nitrates.

5- *Useful* in Prophylaxis of Angina Pectoris:
a- Useful in Stable & Unstable angina. Better use cardio-selective β_1-blockers.
b- Non-selective β-Blockers are Contraindicated in Variant (Prinzmetal) angina.
c- Can be combined with Nitrates & Nifedipine:
- Nitrate & Nifedipine → Coronary VD + ↑ HR + ↓ Diastolic filling + ↓ EDV + ↓ Ejection time.
- β-Blockers → No VD + ↓ HR + ↑ Diastolic filling + ↑ EDV + ↑ Ejection time.

d- ***NOT*** combined with Verapamil → Severe cardiac inhibition.

6- *Adverse Effects* & *Contraindications* (See A.N.S.).

IV- Anti-Platelet Drugs

1- Dipyridamol *(Persantin)*:

1- ↓ Phosphodiesterase enzyme → ↑ cAMP → ↓ Platelet aggregation.
→ ↑ Heart → +ve Inotropic effect.
→ Blood vessels → V.D.
2- ↓ Uptake & ↓ Degradation of Adenosine → ↑ Adenosine → V.D.
3- Coronary V.D. especially small coronaries.
4- ↑ Heart: ↑ cAMP & reflex from ↓ Bl.p.
5- Dipyridamol does ***NOT*** correct myocardial ischemia.
6- Used as *Anti-platelet* → ↓ Conversion of Stable to Unstable Angina.

2- Aspirin in SD (75–150 mg) → ↓ Platelet TXA-2. Also treats Nitrate-induced headache

3- ADP-Receptors Blockers: Ticlopidine & Clopidogrel.

4- GP IIb/IIIa-Receptors Blockers: Abciximab & Tirofiban.

N.B.)

A) Favorable Anti-Anginal Combinations:

1- Nitrate or Nifedipine → Coronary VD + ↑ HR + ↓ Diastolic filling + ↓ EDV + ↓ Ejection time.
β-Blockers → No VD + ↓ HR + ↑ Diastolic filling + ↑ EDV + ↑ Ejection time.
2- Nitrates → Coronary VD + Veno-dil + ↓ Preload + ↑ HR + ↓ Diastolic time
Verapamil → Coronary VD + Arterio-dil + ↓ Afterload + ↓ HR + ↑ Diastolic time.

B) Unfavorable Anti-Anginal Combinations:

1- Nitrate + Nifedipine → Severe Hypotension & Tachycardia.
2- β-Blockers + Verapamil → Severe Cardiac Inhibition.
3- Do *NOT* use 2 drugs of the same class in the same line of treatment.

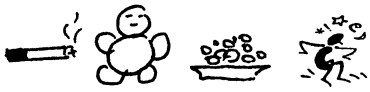
C) Choice of Treatment:

Patient	Useful Drugs	Drugs Contraindicated
1- Variant Angina	Nitrates & CCB	Non-selective β-Blockers
2- Angina + B.A., P.V.D. or D.M.	Nitrates & CCB	Non-Selective β-Blockers
3- Angina + H.B. or H.F.	Nitrates & Nifedipine	β-Blockers & Verapamil

Management Of Angina Pectoris

A) Angina of Effort (Classic, Stable):

I- General Measures:



1- *Change Bad Habits*: Stop smoking, Weight reduction & Gradual exercise.
2- *Avoid*: Exertion, emotions, eating heavy meals & exposure to cold.
3- *Treat*: Hypertension, Diabetes mellitus & Hypercholesterolemia.

II- Drug Treatment:

A) Acute Attacks (Present Pain) & Immediate Prophylaxis:
Rapidly acting Nitrates:

1- Nitroglycerine S.L. 0.5 mg or Buccal Spray 0.4 mg
2- Isosorbid Dinitrate S.L. 5 mg or Buccal Spray 1.25 mg

In Acute Attack (pain) → Repeat the drug every 5 min. till disappearance of pain or maximum 3 doses, otherwise → Acute Myocardial Infarction.

In Immediate Prophylaxis → Drugs are taken 5 minutes before exertion.

B) Long Term Prophylaxis:

1- Long Acting Nitrates: Oral S.R., Trans-dermal patch or Ointment.
And / or
2- Calcium Channel Blocker
And / or
3- β-Blocker
And / or
4- Nicorandil

C) Anti-Platelet Drugs:

1- Aspirin 75 – 150 mg / day orally
2- Dipyridamol 75 mg tds orally

B) Variant Angina

* Treatment of Acute tacks & Prophylaxis:

1- Nitrates and / or Calcium Channel Blocker.
2- Avoid Non-selective β-Blockers

C) Unstable Angina

1- Hospitalization.
2- Nitroglycerine S.L., Spray, I.V. then Oral & Transdermal.
3- Nifedipine
4- Cardio-selective β_1-Blocker with***out*** I.S.A. e.g. Atenolol.
5- Anti-Thrombotics → Aspirin & Heparin
6- Coronary Artery Reperfusion Surgery.

Myocardial Infarction

Death of an area of myocardium due to prolonged ischemia, more than 15 minutes, induced by coronary thrombosis or spasm.

* Cause of Death from Myocardial Infarction :

1- Mechanical failure → Heart failure → Cardiogenic shock.
2- Ventricular arrhythmias → Fibrillation.

* Role of Calcium :

1- Ischemia → Initial ↑ intracellular calcium due to ↓ of ATP-dependent :
   a- Calcium uptake by sarcoplasmic reticulum.
   b- Sodium efflux → ↓ Sodium / Calcium exchange.
2- ↑ Intracellular Calcium causes :
   a- Death of cells due to ↑ activity of intracellular calcium-dependent proteases.
   b- ↑ Tendency to dysrhythmias.

* Lines of Treatment of Myocardial Infarction :

Transfer the patient to nearest IUC or CCU.

A) Before and During Transfer :

1- Cardio-pulmonary resuscitation (**C.P.R.**) if cardiac arrest.
2- Oxygen and IV fluids, **ONLY** when required.
3- **Nitroglycerin** :
   a- Sublingually up to 3 doses with 5 minutes interval in-between.
   b- Percutaneous (Transdermal) patch.
4- **Morphine sulfate** for severe pain and / or pulmonary edema.
5- **Frusemide** (20 mg/5 min IV) if acute pulmonary edema with normal Bl.p.
6- **Digoxin** (0.5 mg IV) if lung congestion and rapid declining Bl.p.
7- Saline by rapid IV Infusion **if Bl.p.** is rapidly declining and lungs are free.

B) At the Intensive (Cardiac) Care Unit (ICU & CCU) :

1- **Thrombolytic (Fibrinolytic)** Therapy within the first 6 hours to dissolve the thrombus :
   a- *Recombinant Tissue Plasminogen Activator (rTPA = Alteplase)* :
      IV 10 mg bolus then 50 mg over 1st hour then 40 mg over 2 hours.
   b- *Streptokinase* 1.5 million units in 200 ml saline IV infusion as single dose.
2- **Heparin** to prevent extension or recurrence of the thrombus. Dose 24'000-30'000 U/day during the whole hospital stay. Given either as IV drip (1000-1200 U/hour) or IV bolus 5000 U/4-6 hours.
3- **Nitrates** → Veno-dilator → ↓ Venous return → ↓ Preload & lung congestion.
4- **Opiates** e.g. IV Morphine sulfate :
   a- Relieve the pain.
   b- Reduce apprehension.
   c- Reduce Pre- & After-loads : Veno-dilator, ↓ Sympathetic & Histamine release.
   d- Reduce excess tachypnea induced by pulmonary edema with Acute HF.
5- Oxygen **when** indicated. Oxygen can induce arterial VC → ↑ TPR → ↑ Afterload.
6- **β-Blockers** from the 1st day : ↓ Cardiac work → Cardio-protective → ↓ Re-infarction.
7- **Calcium Channel Blockers (CCB)** : To prevent ↑ intracellular Calcium → Cardio-protective → ↓ Arrhythmia and irreversible cardiac cell damage.

Hypertension ارتفاع ضغط الدم

Sustained elevation of Systemic Arterial Blood Pressure ≥ 140 / **90**

* Types of Hypertension:

1- Primary (Idiopathic, Essential): 90 - 95% of cases, of Unknown cause.

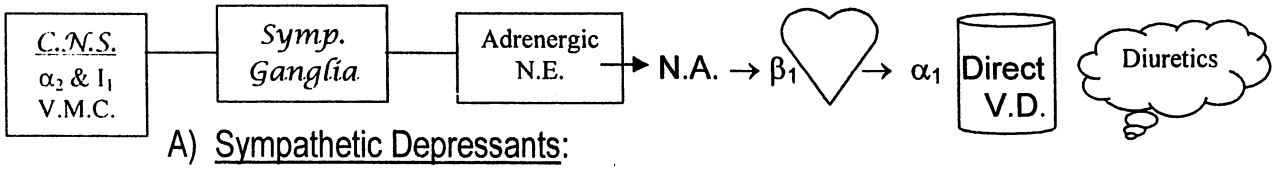
2- Secondary: 5 - 10% of cases, of known cause e.g.
- Renal artery stenosis.
- Pheochromocytoma.
- Drugs: Corticosteroids, Contraceptives, Clonidine withdrawal & Cheese reaction with MAO.I.

* Classification of Hypertension According to Diastolic Blood Pressure (DBP):

1- Mild:	90	-	104	mm Hg.
2- Moderate:	105	-	114	mm Hg.
3- Severe:	> 115			mm Hg.
4- Malignant:	> 130 mm Hg	+	Papilledema.	

Anti-Hypertensive Drugs

NB) *Control of Arterial Bl.p.: T.P.R. + C.O.P. (Heart & Blood Volume)*



A) Sympathetic Depressants:

1- **Central Sympathoplegic Drugs**:
- a- α_2-Agonists: α-Methyl-Dopa & Clonidine.
- b- Imidazoline I_1-Agonists: Clonidine, Moxonidine & Rilmenidine.
- c- Depressants of V.M.C.: Reserpine.

2- **Ganglion Blockers**: Trimethaphan.

3- **Adrenergic Neuron Depressants**: Guanethidine & Reserpine.

4- **Adrenoceptor Blockers**:
- a- α-Blockers: Prazosin.
- b- β-Blockers: Propranolol & Atenolol.
- c- α & β - Blockers: Labetalol & Carvedilol.

B) Direct Vasodilators:

1- **Arterio-dilators**: Hydralazine, Minoxidil, Diazoxide & C.C.B.

2- **Veino-dilators**: Nitrites & Nitrates.

3- **Mixed dilators**: Na Nitroprusside & ACE Inhibitors.

C) Diuretics:

1- **Thiazides**: Hydrochlorothiazide.

2- **Loop**: Frusemide.

3- **K^+-Retaining diuretics**: Spironolactone.

D) Anxiolytic Drugs: e.g. Benzodiazepines

Anxiety → Sympathetic → Hypertension → Anxiety

N.B.)

1- ***ONE*** drug may act on ***MORE*** than one site of action.

2- ***RAPID*** lowering of Bl.p. in ***SEVERE*** hypertension may be ***FATAL*** due to:
   a- Renal failure. b- Intravascular thrombosis.

3- For each ***GROUP*** of drugs mention:
   a- Example for this group.
   b- Mechanism of action.
   c- Main advantages.
   d- Main disadvantages.
   e- Use in hypertension especially the presence of another indication.

4- ***Postural Hypotension***:
   a- Veino - Dilators e.g. Nitrates.
   b- Depressants of Peripheral Sympathetic Postural Reflexes:
      - Ganglion Blockers. - Guanethidine. - Alpha - Blockers.

I- *Sympathetic Depressants:*

A) Adrenergic Receptor Blockers:

1- Alpha Blockers:

1- Example: *Prazosin.*

2- Mechanism of Action:

a- Selective α_1-blocker. } V.D

b- Direct VD: ↓ Phosphodiesterase: }

- ↑ cAMP → ↑ H.R. + V.D.
- ↑ cGMP → ↓ H.R. + V.D.

c- Potent Mixed Dilator →
- Art. VD → ↓ TPR → ↓ After-load & ↓ Bl.p.
- Vein. VD → ↓ VR → ↓ Pre-load & ↓ COP → ↓ Bl.p.
- Lowers BOTH SBP & DBP.

3- Advantages: a- Potent. b- NO uncomfortable Tachycardia. WHY?

4- Disadvantages:

a- Initial Syncopal attack (First Dose Phenomenon). How to avoid?

b- Alpha Blocker → Nasal congestion, Failure of ejaculation & Postural hypotension.

c- Na^+ & H_2O retention. Add diuretic.

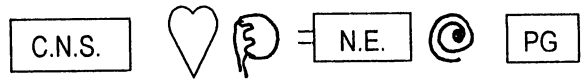
5- Used in Hypertension especially + P.V.D., C.H.F., B.P.H. & Pheochromocytoma

2- Beta Blockers:

1- Examples:

a- Selective β_1 - Blockers: *Atenolol.*

b- Non-selective β - Blockers: *Propranolol.*



2- Mechanism of Action: Effect appears after *4 WEEKS* of continued use:

a- ↓ Sympathetic outflow from CNS. b- ↓ C.O.P. c- ↓ Renin.

d- ↓ Release of Noradrenaline. e- Resetting of Baroreceptors. f- ↑ PG.

3- Advantages:

a- No postural hypotension.

b- Prevent tachycardia induced by hypotensive drugs

b- Decreases cardiac work (Cardio-protective).

4- Disadvantages of β-Blockers:

a- Block of β_1-receptors → ↓ HEART → -ve Ino , -ve Chrono , -ve Dromo.

b- Block of β_2-receptors:

- Worsens Variant (Prinzmetal) Angina.
- Lung: Bronchospasm.
- Liver: ↓ Glycogenolysis.
- Liver: ↓ Hepatic blood flow by 30% → Enzyme Inhibition.
- Limbs: Cold extremities & Intermittent claudication.

c- Metabolic → Hypoglycemia, ↑ Triglycerides & ↑ K^+.

d- CNS: Lipophilic β-blockers → Sedation, depression, night mares & vivid dreams.

e- Sudden Stop → DEATH.

5- Used in Mild & Moderate Hypertension:

a- Young age hyperactive. b- High renin.

c- Presence of other indication of β-Blockers e.g. Angina, Arrhythmia or Hyperthyroidism.

3- *Concurrent α + β - Blockers:*

1- Example: *Labetalol.*

2- Mechanism:

a- α_1-Block → V.D. → ↓ T.P.R.

b- β_1-Block → ↓ Renin

c- β_2-Partial Agonist → V.D.

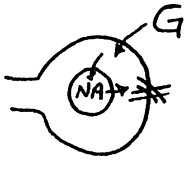
3- Advantages:

a- NO uncomfortable Tachycardia. b- NO ISA & NO ↓ COP.

4- Disadvantage: Postural Hypotension.

5- Used in Moderate hypertension especially in Pheochromocytoma or PVD.

N.B.) *Carvedilol* → Similar to Labetalol + Anti-oxidant.



B) Adrenergic Neuron Depressants:

1- *Guanethidine:*

1- Mechanism: Inhibits the ***RELEASE*** of endogenous Noradrenaline.

2- Advantages: Does NOT pass BBB → NO Parkinsonism or Psychic Depression.

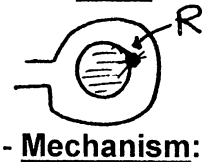
3- Disadvantages:

1- Postural Hypotension. How to predict & avoid?

2- Nasal congestion. 3- Parotid pain. 4- Bradycardia.

5- Diarrhea. 6- Failure of ejaculation.

4- Used in SEVERE hypertension specially if accompanied by Parkinsonism or Depression.



2- *Reserpine:*

1- Mechanism: ***DEPLETION*** of Central & Peripheral Catecholamines & Serotonin.

2- Disadvantages: ***P***sychic depression, ***P***arkinsonism & ***P***eptic ulcer.

C) Central Sympathoplegic Drugs:

* Mechanism of Action:

1- α_2-**Agonists**: *α-Methyl-Dopa & Clonidine* → ↓ Sympathetic outflow *But* → Sedation
2- **Imidazoline I_1-Agonists**: *Moxonidine* → ↓ Sympathetic outflow & *Less* sedation.
3- **Reserpine** → ↓ V.M.C. *But More* sedation.

1- α-Methyl Dopa (Aldomet):

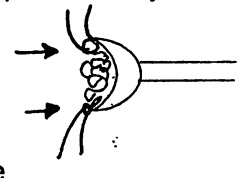
1- Mechanism:

1- **Prodrug**: α-Methyl dopa —*Decarboxylase*→ α-Methyl Dopamine —*β-Hydroxylase*→ α-Methyl Noradrenaline → α_2-Agonist →
   a- ***Central*** → ↓ Sympathetic outflow from C.N.S. = ***Main Mechanism***
   b- Presynaptic → ↓ Release of Noradrenaline.
   c- Kidney → ↓ Release of Renin.
2- Inhibits the synthesis of Catecholamines & Serotonin.

2- Advantages: Maintains R.B.F.

3- Disadvantages:

a- Allergy (Hypersensitivity): Hemolytic anemia (+ve Coombs' test) & Hepatotoxicity.
b- CNS: Sedation, Depression & Parkinsonism (Less than Reserpine)
c- Bradycardia & Postural Hypotension (Less than Guanethidine).
d- Fluid retention → Pseudo-tolerance. Add Diuretic.
e- Dry mouth & Constipation.
f- Endocrine → ↑ Prolactin → Galactorrhea, Gynecomastia & Impotence.



4- Used in Hypertension especially:
a- High renin. b- Renal insufficiency. c- Pregnancy.

2- Clonidine:

1- Mechanism:

a- α_2-Agonist → *Central* ↓ Sympathetic, *Presynaptic* ↓ Noradrenaline & *Kidney* ↓ Renin.
b- Imidazoline I_1-Agonist → *Central* ↓ Sympathetic tone.

2- Advantages: Maintains RBF.

3- Disadvantages:

a- If used in Large Dose or IV → Initial Hypertension.
b- Sudden Stop → Severe HYPERTENSION.
Treat by either reuse Clonidine or give α-blocker ± β-Blocker.
c- Similar to methyl-dopa:
- Sedation & Depression. - Dry Mouth (Xerostomia).
- Bradycardia. - Constipation. - Impotence.

4- Used in Hypertension specially: a- High renin. b- Renal insufficiency.

3- Guanfacin: Similar to Clonidine BUT: Less Sedation & Less Withdrawal Hypertension
4- Guanabenz: α_2-Agonist + Natriuretic → NO Pseudotolerance.

E) Competitive Ganglion Blockers:

1- Example: ***Trimethaphan***
2- Mechanism: a- Ganglion Blocker. b- Histamine Releaser. c- Direct VD.
3- Disadvantages: a- Severe Hypotension. b- Intravascular thrombosis. c- Renal Failure.
4- Use: ***IV Infusion*** in ***EMERGENCY*** Hypertension e.g. Hypertensive Encephalopathy.

II- Vaso - Dilators

* Classification:

A) Direct Vasodilators:

1- ***Veno*** - Dilators: Nitrites & Nitrates. (See Angina).
2- ***Arterio*** - Dilators: Hydralazine.
3- ***Mixed*** Dilators: Na Nitroprusside.

B) Others:

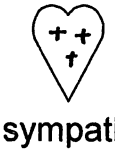
They modulate (simulate or stimulate or block) endogenous mediators.

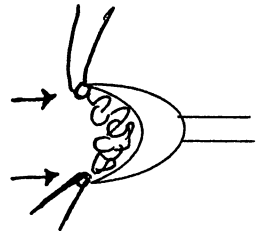
1- *Renin-Angiotensin Antagonists*: Captopril.
2- *Most of Autacoids*: Histamine & Bradykinin
3- *Sympathomimetics*: β_2-Agonists (Nylidrine & isoxsuprine)
& D_1-Agonists (Fenoldopam).
4- *Sympathetic Depressants* e.g. α_1-blockers, Prazosin.
5- *Parasympathomimetics* e.g. Methacholine.

N.B.)

1- Arteriolar VD:
a- ↓ Total Peripheral resistance (TPR).
b- ↓ Blood pressure (DBP > SBP).
c- ↓ After - load on heart.
d- ↑ Stroke volume & ↑ COP specially in HF.

2- Veinular VD:
a- ↓ Venous Return (VR).
b- ↓ End Diastolic Volume (EDV).
c- ↓ Pre-load on the heart.
d- ↓ COP:
- ↓ Bl. p. (SBP).
- ↓ Renal Blood Flow (RBF).
- Postural Hypotension.





3- ANY VD → ↓ Bl.p. → ↑ Reflex sympathetic →
1- ↑ Heart → +ve Ino & +ve Chrono → ↑ Cardiac Work & ↑ O_2 needs → ***Angina***.
(ADD β-blocker)
2- ↑ Renin → ↑ Angiotensin → ↑ Aldosterone → Na^+ & H_2O Retention → ***Edema***.
Also VD of Efferent arterioles → ↓ Filtration pressure → ↓ GFR ------→ ***Edema***.
(ADD DIURETIC).

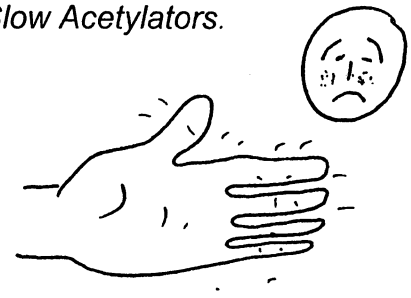
1- Hydralazine (Apresoline):

1- Direct **ARTERIOAR** VD. May act through release of NO.

a- Coronary, Splanchic & Renal VD → ↑ RBF.

b- ↓ TPR → ↓ Bl.p. (DBP > SBP), ↓ After-load & ↑ Stroke volume & ↑ COP in HF.

2- Disadvantages → *Especially in Large dose & Slow Acetylators.*



a- ↓ Bl.p. → ↑ Sympathetic →

- ↑ Heart → Tachycardia & Angina. ***(ADD b-Blocker)***
  Hydralazine in C.I. in Angina pectoris & Arrhythmia.
- Kidney → ↑ Renin → Edema. ***(ADD Diuretic).***

b- VD → Headache, Congestion & Flush.

c- Orally → GIT upsets.

d- Hypersensitivity (Allergic) Reactions:

- ***Reversible Rheumatoid arthritis & Lupus erythematosis-like syndrome.***
- Skin rash & drug's fever.

e- Peripheral neuritis: Treat by Vit B_6 (*10-50 mg / day).*

3- Therapeutic Uses:

1- Hypertension (ADD β-blocker & Diuretic). 2- Heart Failure.

2- Minoxidil (Loniten):

1- Minoxidil **(Prodrug)** → Minoxidil Sulfate (Active Metabolite) → Activate K^+-Channel → Hyperpolarization.

2- Potent, Oral, Long acting, Direct Art. VD → ↓ TPR, ↓ DBP > SBP, ↓ After-load & ↑ COP especially in Heart Failure.

3- ***Disadvantages***:

a- ↓ Bl.p. → ↑ Sympathetic:

- ↑ Heart → Tachycardia & Angina. ***(C.I. in Anglia & Arrhythmia, ADD β-Blocker).***
- Kidney → ↑ Renin → Edema (Pericardial effusion). ***(ADD Loop Diuretic).***

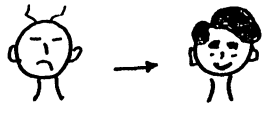
b- Hypertrichosis.

4- ***Therapeutic Uses***:

a- Severe Hypertension (ADD β-blocker & Loop Diuretic).

b- Resistant Heart Failure.

c- Locally in Alopecia (Regain Lotion & Cream).



3- Diazoxide (Hyperstat):

1- Direct Arteriolar VD. Activates K^+-Channels.

2- Related to Thiazide Diuretics.

3- Disadvantages:

a- ↓ Bl.p. → ↑ Reflex Sympathetic →

- ↑ Heart → Tachycardia & Angina. ***(ADD β-Blocker).***
- Kidney →↑ Renin → Edema. ***(ADD Diuretic).***

b- Like Thiazides → ***Hyperglycemia*** (↓ Insulin release) ***& Hyperuricemia.***

4- Used:

a- ***EMERGENCY*** *Hypertension*: Diazoxide is highly bound to plasma proteins so given by either:

- Rapid IV injection of large dose.
- Repeated IV injection of small doses till saturation of plasma proteins, then IV Infusion.

b- Orally in Hypoglycemia due to *Insulinoma*.

4- Calcium Channel Blockers (CCB): (See angina)

1- Dihydropyridines: Nifedipine, Amlodipine & Felodipine → **V.D.** > ↓ Heart.
2- Verapamil & Diltiazem → ↓ **Heart** > V.D.
3- Others: Indapamide → Thiazide analogue. Used in sub-diuretic dose.

5- Na Nitroprusside (Nipride):

1- Very Powerful ***MIXED (Balanced)*** VD.

2- Mechanism of Action:

Nitroprusside → RBCs & Endothelium → NO → ↑ Guanylate Cyclase → ↑ cGMP:
a- Mixed Balanced (Arteriolar = Venular) VD.
b- ↓ Platelet aggregation.

3- A c t i o n s:

a- Art. VD → ↓ TPR → ↓ After-Load → ↓ Bl.p.
b- Vein. VD → ↓ VR → ↓ EDV → ↓ Pre-load → ↓ Bl.p.
c- COP is maintained due to ↓ TPR. It may ↑ in patients with H.F.

4- Pharmacokinetics:

a- Used by ***IV Infusion***. *Onset : 1/2 min. Peak : 2 min. Duration : 3 min.*
b- Nitroprusside → RBCs & Endothelium → NO + Cyanide.
c- Cyanide → Liver Rhodanase enzyme → Thiocyanate.
d- Thiocyanate is excreted in urine.

5- Disadvantages of Nitroprusside:

a- Large dose → Severe Hypotension & Shock.
b- Sudden Stop → Rebound Hypertension.
c- Prolonged Use especially in old age → Accumulation of:
- Cyanide → Acidosis & arrhythmia → DEATH *(Add Thiosulfate or Hydroxocobalamine)*
- Thiocyanate → Delirium & Psychosis.

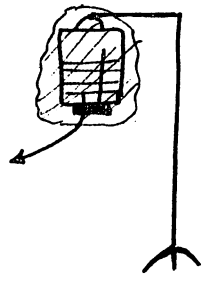
d- Teratogenic.

6- *Therapeutic Uses of Nitroprusside*:

a- Emergency Hypertension e.g. Hypertensive Encephalopathy.
b- Emergency Heart Failure (Acute left ventricular failure & Pulmonary Edema).
c- Controlled hypotension during plastic & neuro-surgery.
d- Acute aortic dissecting aneurysm (with β-Blockers).

7- Precautions during Nitroprusside Infusion:

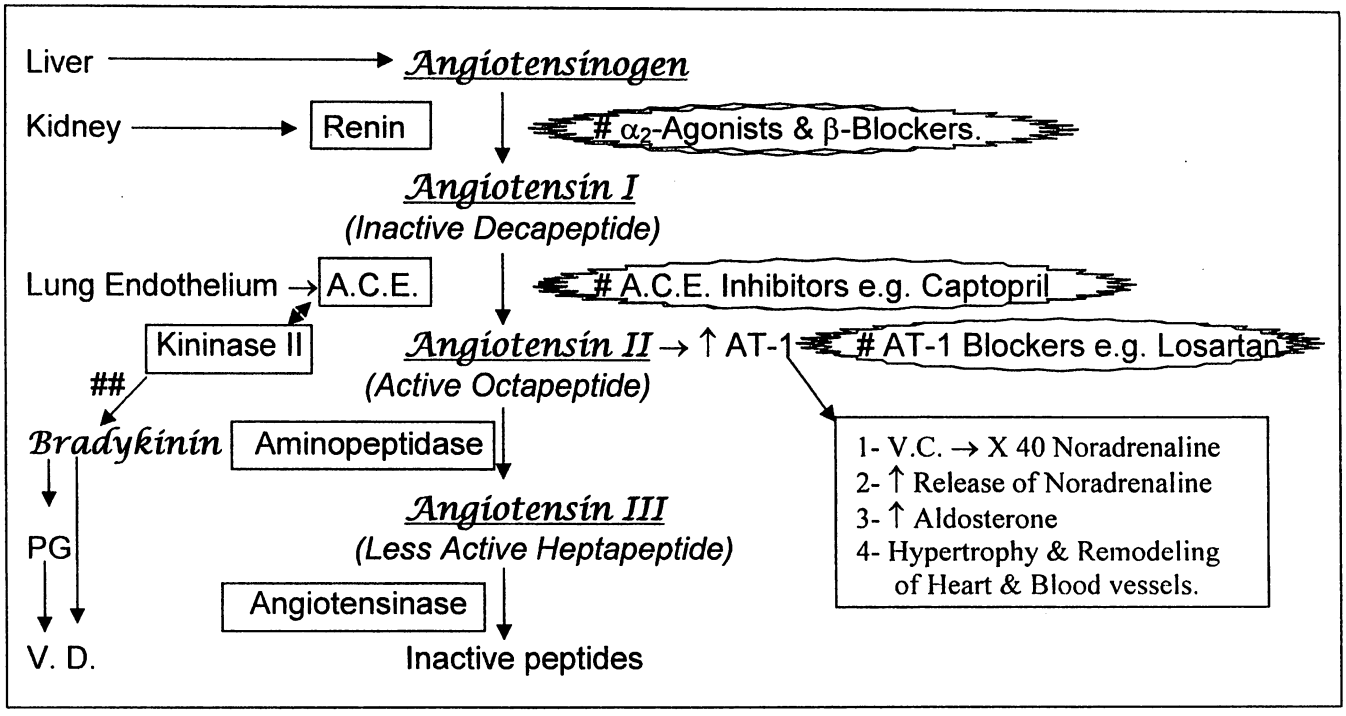
a- Used ONLY by IV Infusion 0.5 – 10 ug / kg / min..
b- Fresh Solution.
c- Cover with Foil (Photosensitive).
d- Continuous monitoring.
e- Never stop infusion suddenly.



6- Ketanserin (Sufrexal):

1- ***5-HT$_2$*** Blocker → Mixed VD & ↓ Platelet aggregation.
2- α_1-Blocker.
3- Useful in: Hypertension & PVD.

7- Renin-Angiotensin Antagonists:



A) Drugs ↓ Release of Renin:

1- β_1-Blockers: Atenolol, Propranolol & Labetalol.

3- α_2-agonists: Clonidine & α-Methyl-Dopa.

B) Renin-receptor Blockers:

1- Examples: ***Enalkiren & Remikiren***.

2- Not very effective in hypertension.

C) Angiotensin Converting Enzyme Inhibitors (ACE.I):

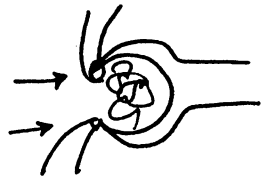
1- Mechanism of Action:

Inhibit Angiotensin Converting Enzyme:

a- ↓ Conversion of inactive Angio I to active Angio II → ↓ Synthesis of Angio II:
- ↓ VC.
- ↓ Aldosterone.
- ↓ Sympathetic.
- ↓ Hypertrophy & Remodeling of heart & BV.
- ↑ Renin & ↑ Angio I.

b- ↓ Inactivation of Bradykinin → ↑ Bradykinin → VD (Directly & by ↑ PGs).

2- Pharmacological Actions of ACE.I:



a- Mixed VD Arterial > Venous.

b- Art. VD → ↓ T.P.R. → ↓ After-load & ↓ Bl.p.

c- Weak Vein. VD → ↓ V.R. → ↓ E.D.V. → ↓ Pre-load & ↓ Bl.p.

d- C.O.P. is maintained or even ↑ in cases of H.F.

e- ↑ RBF ***BUT*** ↓ GFR (Efferent VD) → ↓ Glomerular hypertension.

f- Advantages:
- NO ↓ COP, even it may ↑ COP in HF. } Less Veno-dilator
- NO postural hypotension. }
- NO reflex tachycardia (↓ Baroreceptors reflex & ↓ Sympathetic activity).
- NO abnormality in Glucose or Lipid or Cholesterol or Uric acid metabolism (Better than diuretics).

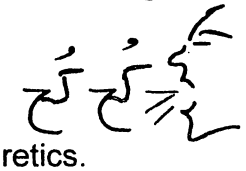
3- Therapeutic Uses of ACE.I:

a- ***Hypertension***, especially:
- High renin.
- Diabetic nephropathy (Very Important).
- Heart failure.
- *But Not* effective in Primary Hyperladosteronism.

b- ***Heart Failure***:
- ↓ BOTH After & Preload → Improve cardiac performance → ↑ COP.
- ↓ Secondary hyperadlosteronism → Natriuretic → ↓ edema.

c- Under trial in Myocardial infarction to decrease the infarct size & # Remodeling of Heart.

4- Side Effects of ACE.I:



a- Dry irritant ***Cough*** due to ↑ Bk & ↑ PGs. Treat by NASID.

b- ***First dose hypotension*** especially in Na^+-depleted patients by diuretics. Treat by NaCl orally or Infusion (Saline). Stop diuretics before the use of ACE.I.

c- ***Hyperkalemia***, especially if accompanied with K^+-retaining diuretics e.g. Spironolactone, β-Blockers & NSAID.

d- ***C.I. in Bilateral Renal Artery stenosis*** → **Fatal Renal Failure.**

e- **C.I.** in 2nd - 3rd trimester of **pregnancy** → Fetal hypotension, renal failure, Oligohydramnios → Malformation or DEATH.

f- ***Proteinuria***: Do frequent urine analysis.

g- ***Neutropenia***: Do frequent blood count.

h- ↓ ***Taste*** (Dysgeusia).

i- ***Allergic*** manifestations *(Especially S-H containing e.g. Captopril)* → Angioedema.

5- *Drug Interactions of ACE.I*:

a- Na^+-depleting diuretics accentuates the initial hypotensive effect.

b- K^+-retaining diuretics e.g. Spironolactone augments the hyperkalemic effect.

c- NASID e.g. aspirin # partially the hypotensive effect by # synthesis of PGs.

6- *Members of ACE.I.*:

* Classification of ACE.I. → S-H Containing → Captopril
* Classification of ACE.I. → Non S-H Containing → Drug → Lisinopril
* Classification of ACE.I. → Non S-H Containing → Prodrug → Enalapril & the Others.

* S-H Containing:

Captopril *(Capoten)*:

1- Active drug.
2- Well absorbed orally, *BUT* affected by food. Taken 1-2 hours before meal.
3- Does not pass BBB.
4- 50% metabolized in liver.
5- 50% excreted unchanged in urine.
6- Short acting. Used bid or tds.
7- Frequent side effects e.g. Angio-edema.

* Non S-H Containing ACE.I.:

- Less side effects than Captopril.
- Longer $t_{1/2}$, used od or bid.
- Oral absorption is not affected by meal.

A) Active Drugs:

Lisinopril *(Zestril)*:

a- Active drug. Longest $t_{1/2}$, used od.

b- NOT metabolized. Excreted as such in urine.

B) Prodrugs → Metabolism → Active metabolites.

1- **Enalapril** *(Vasotec)*:

a- Inactive Prodrug → Active ***Enalaprilat***.

b- More potent than Captopril.

3- **Perindopril** *(Coversyl)* : Prodrug → ***Perindoprilat***.

4- **Benazepril** *(Cibacen)* : Prodrug → ***Benazeprilat***.

5- **Ramipril** *(Atace)* : Prodrug → ***Ramiprilat***.

6- **Quinapril** *(Accupril)* : Prodrug.

7- **Fosinopril** *(Monopril)*:

a- Prodrug.

c- Excreted in bile, not urine. Its dose has not to be readjusted in impaired renal function.

D) Angiotensin II (AT)-receptor Blockers:

★ **Losartan** *(Cozaar, 25-50 mg od)*

★ **Candesartan** *(Atacand, 8 mg od)*

★ **Valsartan** *(Tareg, 80-160 mg od)*

★ **Telmisartan** *(Micardis 40-80 mg od)*

1- *Non-peptide*.

2- *Compete* with Angio II for AT_1-receptors. They are Pure Antagonists. Leading to:

a- ↓ V.C. → V.D. They also release prostacyclin → VD.

b- ↓ Synthesis and release of Aldosterone

c- ↓ Sympathetic : Block of presynaptic AT_1-receptors on adrenergic neurons → ↓ Noradrenaline release.

d- Prevent hypertrophy & Remodeling of Heart & BV due to hypertension.

e- VD of Renal vessels → ↓ Glomerular hypertension (Efferent renal VD).

3- *Metabolic Actions*: Correct side effects of diuretics

a- Potassium retaining effect # Hypokalemia.

b- Mild uricisuric effect # Hyperuricemia.

c- Ameliortae hyperglycemia induced by diuretics.

4- *Therapeutic Uses*: Similar to ACE.I. Effective orally.

5- *Side Effects*: Similar to ACE.I. BUT NO Dry irritant cough.

2- Saralasin :

1- Peptide analogue of Angio II.

2- Partial agonist → Initial hypertension.

3- NOT effective orally. Used by IV Infusion.

4- NOT commonly used clinically.

III- Diuretics:

A) Thiazides & Analogues:

1- Example: Hydrochlorothiazide *(Eidrex)* & **Chlorthalidone** *(Hygroton).*

2- Mechanism of Anti-Hypertensive Effect:

a- Initial ↓ Bl.p. is due to their diuretic effect → ↓ Blood volume.

b- Sustained ↓ Bl.p is Mainly due to Direct Art. VD → ↓ TPR → ↓ DBP & ↓ SBP:

- Activation of K^+-channels → Hyperpolarization.
- Depletion of Na^+ & H_2O from arterial wall → ↓ Edema of arterial wall & ↓ V.C. of Noradrenaline & Angio II.
- V.D. may be through PGs # by NSAID.

3- Therapeutic Uses:

a- Subdiuretic doses in Mild & Moderate hypertension especially in Elderly & C.H.F.

b- Correct edema produced by other anti-hypertensive drugs.

4- Side Effects:

a- ↓ RBF & ↓ GFR.

b- Hypokalemia. c- Hyponatremia. c- Hypchloremic alkalosis. d- Hypomagnesemia.

e- Hypercalcemia. f- Hyperglycemia. g- Hyperuricemia. g- Hyperlipidemia.

h- Hypersensitivity reactions. I- G.I.T. upsets j- Fetotoxic

B) Loop Diuretics:

1- Example: Frusemide *(Lasix).*

2- Mechanism of Anti-Hypertensive Effect:

a- MAINLY by its DIURETIC effect → ↓ Blood volume → ↓ COP.

b- If IV → Veno-Dilation → ↓ VR → ↓ COP.

c- ↑ RBF & ↑ GFR.

2- Therapeutic Uses :

a- Orally in Mild & Moderate hypertension especially if RENAL INSUFFICIENCY.

b- Orally in Severe Hypertension.

c- IV in EMERGENCY Hypertension.

3- Side Effects:

a- Hypokalemia. b- Hyponatremia. c- Hypocalcemia. d- Hypomagnesemia.

e- Hypocalcemia f- Hyperglycemia. g- Hyperuricemia. h- Hyperlipidemia.

i- Hypersensitivity. j- G.I.T. upsets j- Deafness. k- Dehydration.

C) K^+-Retaining Diuretics:

1- Example: Spironolactone *(Aldactone)*

2- Mechanism of Anti-Hypertensive Effect:

a- Aldosterone competitive antagonist.

b- Lowers Bl.p. by its DIURETIC effect ONLY.

3- Therapeutic Uses:

a- Alone in hypertension due to Hyperaldosteronism (either primary or secondary).

b- Combined with Thiazides & Loops to potentiate them & # their hypokalaemic effect.

4- Side Effects;

a- Hyperkalemia. NOT combined with ACE.I or Losartan.

b- C.I. in Renal Impairment.

NB) Triamterene & Amiloride: K^+-Retaining diuretics. Direct Na^+-channel blockers.

* *Causes of Treatment Failure of Hypertension:*

1- Unrecognized cause e.g. Pheochromocytoma or renal artery stenosis.
2- Incorrect choice of drugs e.g. Thiazide diuretic in patient with renal impairment.
3- Inadequate dose of drugs.
4- Patient non-compliance.
5- Excess salt intake.
6- Drug interaction e.g. NSAID, Cold remedies (Sympathomimetic V.C. → Nasal decongestants), contraceptives & corticosteroids.

* *Anti-Hypertensives & R.B.F.:*

1- ↑ R.B.F.: Loop diuretics, V.D., ACE.I. & AT-1 blockers.
2- ↓ R.B.F.: Thiazide diuretics & β-Blockers.

* *Anti-Hypertensives & Renin Activity:*

1- ↑ Renin: V.D., ACE.I., AT-1 blockers, α-blockers, ↑ cAMP (β-agonists & PDE inhibitors) & most of diuretics.
2- ↓ Renin: β-blockers & α-2 agonists.

* *Anti-Hypertensives* that ↓ Sympathetic activity → ↓ Sexual function.

* *Choice of Anti-Hypertensive in Special Cases:*

Special Case	Drugs Indicated	Drugs Contraindicated
1- Elderly: a- Usually systolic Hypertension b- Gentle & gradual ↓ Bl.p. c- Avoid Rapid ↓ Bl.p. d- Avoid postural hypotension	- Diuretics - CCB - β-Blockers if cardiac ischemia - ACE.I. if D.M.	
2- Heart Failure	- Diuretics - ACE.I. & AT-1 blockers	- CCB
3- Cardiac ischemia e.g. Angina pectoris	- β-Blockers - CCB - ACE.I. & AT-1 blockers	- V.D.
4- P.V.D.	- α-Blockers - CCB - ACE.I.	- β-Blockers
5- B.A. & C.O.P.D.	- CCB - AT-1 blockers	- β-Blockers - ACE.I.
6- Renal disease	- Loop diuretics e.g. Frusemide - ACE.I. & AT-1 blockers - Methyldopa & Clonidine	- Thiazide diuretics - ACE.I. & AT-1 blockers in bilateral renal artery stenosis
7- Pregnancy	- α-Methyl-Dopa - Hydralazine	- Diuretics - β-Blockers - ACE.I. & At-1 blockers
8- D.M.	- ACE.I. & AT-1 blockers - CCB	- β-Blockers - Diuretics - Diazoxide

* Treatment of Hypertension:

I- Treatment of ***Cause*** in Secondary Hypertension, if possible.

II- ***Non-pharmacologic Therapy***:

1- Dietary sodium restriction.
2- Weight reduction in obese.
3- Cessation of smoking.
4- Alcohol restriction.
5- Physical exercise.
6- Relaxation therapy.

III- ***Drug Therapy*** :

A) *Mild or Moderate Hypertension (DBP 90-114 mmHg)*:

1- *Start by MONO-therapy*. Use *ONE* drug, either :

a- ***Thiazide*** Diuretic or an analogue (Elderly, Heart Failure), OR
b- ***β-Blocker*** (Young, Anxiety, Angina, Tachycardia), OR
c- ***ACE Inhibitor*** (High renin, Heart Failure, Diabetic Nephropathy) OR
d- ***Ca^{2+} channel-blocker*** (Angina, COPD & Arrhythmia "Verapamil")

NB) Thiazide diuretics &/or β-Blockers are the most commonly used drugs.

2- *Double Therapy*, if Monotherapy fails, *ADD* a second drug e.g.:

a- Thiazide diuretic + β-Blocker. OR
b- Thiazide diuretic + ACE Inhibitor.

3- *Triple therapy*, if double therapy fails, add a third drug e.g.:

- Thiazide diuretic + β-Blocker + VD (e.g. ACE Inhibitor or CCB or Hydralazine or Prazosin)

B) Severe Hypertension (DBP > 115 mm Hg) → Start by *TRIPPLE* Therapy:

- Thiazide Diuretic + β-Blocker + VD (See before).

NB) Alternative Choices :

1- In patients with *RENAL* Impairment change Thiazide diuretics → Loop diuretic.
2- If β-Blockers are contraindicated → α_2-agonist e.g. Clonidine & α-methyldopa.

C) *Hypertension Resistant to Triple Therapy*:

1- Loop diuretic + β-blocker + Minoxidil.
2- Loop diuretic + ACE Inhibitor + Ca^{++} channel-blocker.

D) Hypertensive Emergencies:

1- Diastolic > 130 mm Hg + *COMPLICATION* + End Organ Damage (Encephalopathy, Papilledema, Pulmonary edema or Decreased Renal function) → **Hospitalization** (ICU) → ***Parenteral*** Therapy → ***Na Nitroprusside (IV infusion)***, Nitroglycerin (IV infusion), Loop diuretic (Frusemide IV), Labetalol (IV bolus injections), Trimethaphan (IV infusion), Diazoxide (IV), Hydralazine (IM or IV), Nicardipine & Enalprilat.
"Avoid excessively rapid lowering of BP → Stroke or Myocardial infarction".
2- Diastolic > 130 mm Hg & Non-Complicated → use vigorous ***ORAL*** therapy e.g. Nifedipine SL, Captopril chew the tablet, Clonidine or Prazosin.

E) *Special Cases of Hypertension*:

1- Hypertension + Pregnancy → Methyldopa.
2- Hypertension + COPD → Ca^{++} antagonist.
3- Hypertension + Diabetic → ACE Inhibitors.
4- Hypertension + Renal failure → ACE Inhibitors or Loop diuretic.
5- Hypertension + Heart failure → ACE Inhibitors or Diuretics.

Cardiac Stimulants

1- Sympathomimetics β_1-agonists: Adrenaline, Isoprenaline, Dopamine & Dobutamine.
2- Parasympatholytics: Atropine.
3- Cardiac glycosides (Digitalis).
4- Bipyridines: Amrinone & Milrinone.
5- Methyl-xanthines: Theophylline.
6- Hormones: Thyroxin & Glucagon.
7- Calcium.

Inotropic Agents

- Drugs ↑ Cardiac contractility.
- Useful in treatment of Heart Failure.
- They ↑ Free ionized intracellular Ca^{2+}.

1- β_1-Agonists:

a- Examples: Dopamine, Dobutamine & Prenalterol.
b- Mechanism: ↑ Gs-protein → ↑ Adenylate cyclase → ↑ cAMP → ↑ Ca^{2+}.

2- Phosphodiesterase Inhibitors (PDE-I) → ↑ cAMP → ↑ Ca^{2+}.

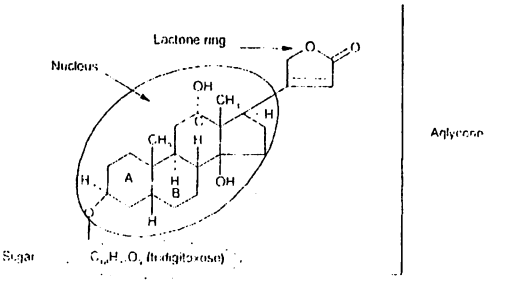
a- Bipyridines e.g. Amrinone & Milrinone → ↓ PDE-III.
b- Methyl-xanthines e.g. Theophylline → ↓ PDE-IV.

3- Direct Activation of Ca^{2+}-Chanels: Some Dihydropyridines.

4- Cardiac Glycosides (Digitalis) → ↓ Na / K ATPase.

Cardiac Glycosides (Digitalis)

- Direct **Inotropic** agents.
- **Plant** origin:
  1- Digitalis purpurea leaves → **Digitoxin**.
  2- Digitalis lanata leaves → **Digitoxin & Digoxin**
  3- Strophanthus gratus seeds → **Ouabain.**



- Cardiac **Glycosides** (Digitalis) on Hydrolysis →
  1- Sugar part (*Glycone*) → Inactive, responsible for *kinetics*.
  2- Non-Sugar part (*Aglycone or Genin*) → *Steroid* →
  Active, responsible for *dynamics* = Actions & Toxicity.
  a- At C_3 – OH to which a sugar (Tridigitoxose) is attached.
  b- At C_{14} – OH.
  c- At C_{17} – Unsaturated Lactone *Ring* (5-6 carbon atoms) = *Cardinolide*.
  - Its saturation → Decreases Activity.
  - Its rupture (opening) → Abolishes activity.

* Kinetics of Digitalis:

1- Absorption:

a- Absorbed orally mainly from upper intestine (*Duodenum*).
b- *Small part of Digitoxin* is absorbed also from the *stomach*.

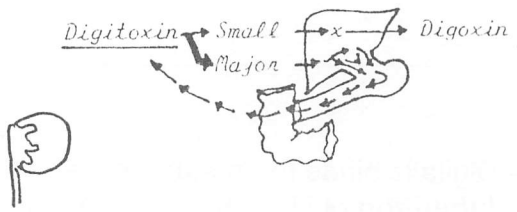
	Ionization	Lipid solubility	Oral Absorption & Administration
1- Digitoxin	Low	High	Well 90-100% Oral → Oral Only
2- Digoxin	Moderate	Moderate	Variable 40-75% → Oral & I.V.
3- Ouabain	High	Low	Unreliable 5-10% → I.V. Only

NB) β-Methyl-Digoxin & Encapsulated hydroalcoholic solution of Digoxin → 100% absorbed orally.

2- Distribution:

a- All over the body & Pass B.B.B.
b- Concentrated in Heart (15-30 times) > plasma → Site of action.
Concentrated in Sk.m. (10-15 times) > plasma → Site of storage.
c- Bound to plasma proteins: Digitoxin (95%), Digoxin (25%) & Oubain (zero%).

3- Fate:



a- Digitoxin → Hepatic Mainly:
- Major part → Entero-hepatic circulation.
- Minor part: Digitoxin (Active) → Digoxin (Active).

b- Digoxin & Ouabain → Renal Mainly.

	Digitoxin	Digoxin	Ouabain
1- Ionization	Least	Moderate	Most
2- Lipid solubility	Most	Moderate	Least
3- Oral absorption	100%	40 – 75%	5 – 10 %
4- Administration	Oral Only	Oral & I.V.	I.V. Only
5- Binding	95%	25 %	Zero %
6- Fate	Hepatic	Renal	Renal
7- t ½	7 days	1.5 days	21 hours
8- Cumulation	Most	Moderate	Least
9- Optimum plasma concentration	10 – 25 ng / ml	0.5 – 2 ng / ml	

* Mechanisms of Action of Digitalis → Vagal & Direct Effects

1- Vagal Effects → ↓ S.A.N., ↑ Atrial Conductivity & ↓ A.V.N.

a- Predominate in Small Therapeutic Doses.
b- Mechanism:
- Sensitizes baroreceptors in aortic arch & carotid sinus → Reflex ↑ Vagal center.
- Direct ↑ Vagal center.
- ↑ Sensitivity of SAN & ANV to Vagal actions.
- Improve circulation in Heart Failure → ↑ COP → # Bainbridge reflex → ↑ Vagal.
*(**NB**) **Bainbridge** reflex = ↓ C.O.P. → ↑ Sympathetic + ↓ Parasympathetic).*

2- Direct (Extra-vagal) Effects:

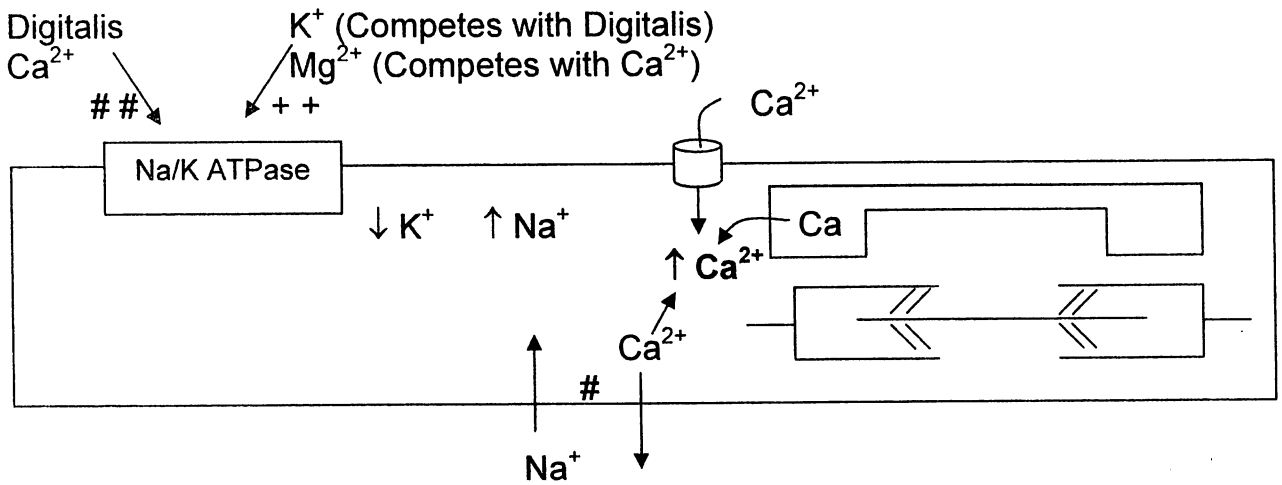
a- Therapeutic dose → +ve Inotropic Effect.
b- Large dose → Direct ↓ S.A.N. & ↓ A.V.N.
c- Toxic dose → ↑ Automaticity especially in Purkinje fibers → Arrhythmia

* Pharmacological Actions of Digitalis:.

A) Cardiac Actions:

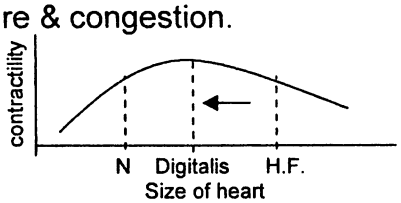
1- ↑ **Contractility = +ve Inotropic** Effect by *Direct Action Only*

* Mechanism of the +ve Inotropic Effect of Digitalis:



1- Digitalis binds to an extracelluar site on the α-subunite of Na^+ / K^+ ATPase → ***Inhibition*** of Na^+ / K^+ ATPase enzyme.
2- K^+ Efflux → ↓ Intracellular K^+ & Na^+ Influx → ↑ Intracellular Na^+.
3- ↑ Intracellular Na^+ → # Passive exchange between Intracellular Ca^{2+} & Extracellular Na^+ → Retention of Ca^{2+}.
4- Activation of Ca^{2+} channels → Ca^{2+} influx.
5- Influxed Ca^{2+} → ↑ Sarcoplasmic retriculum → ↑ Release of Ca^{2+}.
6- ↑ Free ionized intracellular Ca^{2+}.
7- Ca^{2+} → ↓ Troponin & Tropomycin → Sliding of Actin over Myosin → ***+ve Inotropic effect & ↓ Size of Heart.***
8- Digitalis & Ca^{2+} → ↓ ATPase; while K^+ & Mg^{2+} → ↑ ATPase.
9- Excess ↓ of ATPase → Excess Ca^{2+} → Arrhythmia:
   a- Digitalis in Large Dose
   b- Digitalis + ↑ Ca^{2+} or ↓ K^+ (Hypokalemia) or ↓ Mg^{2+} (Hypomagnesemia).
10- Treatment of Digitalis toxicity → Stop Digitalis & Give K^+ or Mg^{2+}.

1- ***+ve Inotropic*** effect *more evident & useful* in patients with *heart failure*.
2- **S**trong **S**hort **S**ystole → Better emptying → ↓ End Systolic volume.
3- *Long Diastole* → Better filling of heart → ↓ Venous pressure & congestion.
4- *↓ Size of heart* → ↓ End diastolic volume → Optimum of Starling's law → Better contractility.
5- *Improve mechanical efficiency of heart* → ↑ C.O.P. (Cardiac work) > ↑ in O_2 consumption.



2- **Bradycardia = -ve Chronotropic** effect by *BOTH* Vagal & Direct effects.

a- ↓ Heart rate especially in Heart failure.
b- Small dose → ↑ Vagal tone Mainly
c- Large dose → ↑ Vagal tone + Direct ↓ SAN → More bradycardia.
d- Atropine can antagonize bradycardia induced by S.D. rather than L.D.

3- **↓ A-V Conduction = -ve Dromotropic** Effect by *BOTH* Vagal & Direct effects.

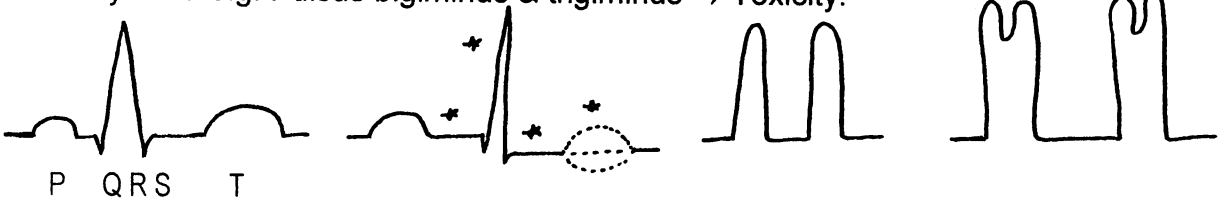
	Vagal	Direct	Result	Refractory Period
1- Atrium	↑ Increase	↓ Decrease	↑ Increase	↓ Shorten
2- A-V system	**↓ Decrease**	**↓ Decrease**	**↓ Decrease by BOTH**	**↑ Prolong by Both**
3- Ventricle	- - -	↑ Increase	↑ Increase	↓ Shorten

4- **Excitability**: S.D. → ↑ Excitability, while L.D. → ↓ Excitability.

5- **Automaticity**: L.D. → ↑ Automaticity specially in Purkinje fibers → Arrhythmia

6- **E.C.G.**:

a- ↓ H.R. = Bradycardia. If less than 60 beats / min. → Toxicity.
b- Long P-R interval, if more than 0.25 second → Heart block → Toxicity.
c- Short Q.R.S. = Short Q-T interval.
d- Depressed S-T segment.
e- Abnormal T-wave → Diminished, abolished or inverted → Toxicity.
f- Arrhythmia e.g. Pulsus bigiminus & trigiminus → Toxicity.



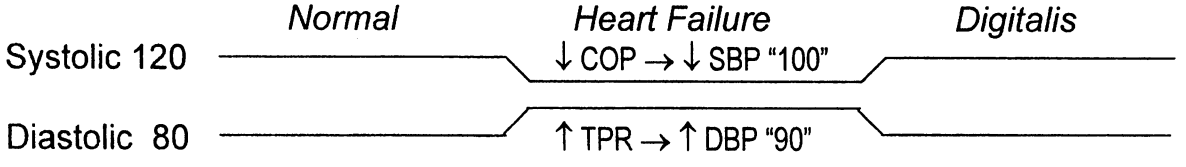
Normal E.C.G. Digitalis E.C.G. Normal Pulse Pulsus Bigiminus

B) Circulation:

1- **C.O.P.**: *(C.O.P = H.R. X S.V.)*

a- H.F. → ↑ Increase due to Better Emptying, Filling & Contractility of Heart).
b- Normal → No effect or may ↓ Decrease due to ↓ H.R. & ↓ S.V. below normal.

2- **Arterial Blood Pressure**: Bl.p. → Systolic (C.O.P.) / Diastolic (T.P.R.)



a- Heart Failure → Normalization → ↑ Systolic (↑ COP) & ↓ Diastolic (↓ TPR).
b- Normal → No effect. L.D. → Hypertension (↑ VMC & Direct V.C.)

3- **Venous Pressure**:

a- Heart Failure → ↓ Decrease → Relieve Systemic & Pulmonary congestion.
b- Normal → No effect.

4- **Coronary circulation** → No effect. Toxic dose → May cause coronary V.C.

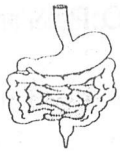
5- **Blood Coagulation** → No Effect.

6- **Blood Volume** → ↓ Decrease Blood volume in Heart Failure ONLY.

C) *Kidney* → Diuretic Effect in Heart Failure ONLY

1- An action on Heart & Circulation = Extra-Renal effect.
2- In Heart Failure: Digitalis → +ve Ino → ↑ C.O.P. → ↑ R.B.F. →
   a- ↑ G.F.R. → ↑ Urine formation.
   b- ↓ Renin → ↓ Angiotensin → ↓ Aldosterone → No Na & Water retention.

D) G. I.T. → Nausea & Vomiting.



a- In early dose → Local irritation.
b- After full digitalization → ↑ C.T.Z. → Toxicity.

E) C.N.S. → Stimulation

a- ↑ Vagal Center, ↑ V.M.C. & ↑ C.T.Z.
b- Toxic doses especially in elderly → Confusion & Hallucinations.

6- Endocrine:

Digitalis → Steroid = Sex hormones → May cause gynecomastia in Male patients

N.B.) Heart Failure

Weak Contractility → ↓ C.O.P. →

1- *Compensatory Mechanisms*:
   a- Hypertrophy & Dilatation *But* → ↑ E.D.V. → ↑ Pre-load.
   b- ↑ Sympathetic → +ve Ino *But* ↑ H.R. & V.C. → ↑ TPR → ↑ After-load.

2- *↓ R.B.F.* →
   a- ↓ G.F.R. → ↓ Urine Formation. } Edema, Hypervolemia
   b- ↑ Renin → ↑ Angio → ↑ Aldo → Na + Water retention. } ↑ E.D.V. & ↑ Pre-load

3- *↑ Residual blood in heart* → Venous congestion:
   a- Right-sided heart failure → Systemic congestion → Liver & Neck veins.
   b- Left-sided heart failure → Pulmonary → Dyspnea.

* Therapeutic Uses of Digitalis:

(3 F "Failure, Fibrillation & Flutter" + PAT)

A) Heart Failure (H.F.):

1- Beneficial Effects:

a- **+ve Inotropic** effect → **↑ C.O.P.** & Improves Mechanical efficiency of heart.
b- ↓ Heart rate & size.
c- Normalizes Arterial Bl.p. } Dew to ↓ compensatory mechanisms
d- ↑ R.B.F. → ↑ Urine formation → ↓ Edema, ↓ Blood volume & ↓ Body weight.
e- ↓ Venous pressure & congestion.

2- Digitalis is effective in Right-, Left- & Both-sided H.F. regardless the cause.

3- Digitalis is *More* effective in:

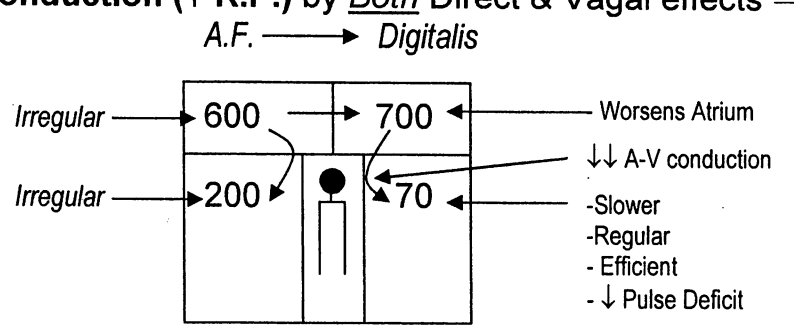
a- H.F. + Atrial Fibrillation → Digitalis is the *Drug of Choice*.
b- H.F. due to *Chronic overload* e.g. Hypertension & Atherosclerosis.

4- Digitalis is Less effective in:

a- Exhaustion of energy stores e.g. Cardiac ischemia.
b- Damaged cardiac muscle e.g. Cardiomyopathy & Myocarditis.

B) Atrial Fibrillation (A.F.):

1- Digitalis is indicated in A.F. whether alone or with H.F.
2- Digitalis *Worsens* the Atrium.
3- *Beneficial* effect → ↓ **A-V Conduction (↑ R.P.)** by *Both* Direct & Vagal effects → Protect the ventricles.
4- Ventricles will be:
   a- Slower.
   b- More Regular.
   c- More Efficient.
   d- Eliminate Pulse deficit.



C) Atrial Flutter:

1- Digitalis may worsens the Atrium: Flutter → Fibrillation.
2- *Beneficial* effect → ↓ **A-V Conduction (↑ R.P.)** by *Both* Direct & Vagal effects → Protect the ventricles → ↓ Ventricular rate & Improve cardiac function.
3- After controlling the ventricular rate → Stop Digitalis:
   a- Normal sinus rhythm.
   b- Persisted Fibrillation. } Give *Quinidine* → Medical Cardio-version.
   c- Return to Flutter. } Quinidine alone may ↑ A-V conduction → Worsens the Ventricles.

D) Paroxysmal Atrial (Supra-ventricular) Tachycardia (PAT):

1- Can be terminated by Digitalis.
2- ↓ A-V conduction → Protect the ventricles.

* Preparations & Dosage of Digitalis:

	Ouabain	Digoxin	Digitoxin
1- Optimum Plasma concentration:		0.5 – 2 ng / ml	10 – 25 ng / ml
2- Initial Dose: a- I.V.	0.25 mg	0.5 – 1 mg	- - -
b- Oral	- - -	0.75 – 1.5 mg	0.8 – 1.2 mg
3- Maintenance Dose Oral:		0.125 – 0.5 mg	0.05 – 0.2 mg
4- T 1 / 2		1.5 days	7 days

A) Initial Digitalizing Dose Followed by Maintenance Dose:

I- Initial Digitalizing (Loading) Dose:

- Either I.V. (Digoxin or Ouabain) or Oral (Digoxin or Digitoxin)
- No history of recent previous digitalization within 2 weeks.
- No hypokalemia.
- Decrease the dose in Elderly.

1- **Ouabain**: I.V. Only → 0.25 mg

2- **Digoxin**:

a- I.V. (0.5-1 mg): 0.5 mg slowly I.V. then 0.25 mg / 2-4 hours.

b- Oral (0.75-1.5 mg): 0.5 mg then 0.25 mg / 6 hours.

3- **Digitoxin**: Oral Only → 0.8-1.2 mg → 0.2 – 0.3 mg / 6 hours.

II- Maintenance Dose:

1- **Digoxin**: 0.125 – 0.5 mg / day Orally

2- **Digitoxin**: 0.05 – 0.2 mg / day Orally.

- Daily Oral Small Dose used after the initial digitalization to replace eliminated digitalis in order to maintain the optimum plasma concentration.
- Digoxin or Digitoxin.
- If the cause of H.F. is Not corrected → Life long use of Digitalis.
- Re-adjust the maintenance dose after 4 – 5 t½
  Digoxin → Week, Digitoxin → Month.
- Look for:
  1- Signs of Improvement:
  a- Chest: ↓ Heart rate, ↓ Heart size & ↓ Dyspnea.
  b- Abdomen: ↓ Liver size & congestion, and ↓ Ascites.
  c- ↓ Edema, ↓ Body weight & ↑ Urine formation.
  2- Manifestations of Toxicity:
  a- Bradycardia < 60 beats / minute or arrhythmia.
  b- Nausea & vomiting.
  3- Monitor plasma level of Digitalis.

B) Non-Loading Method:

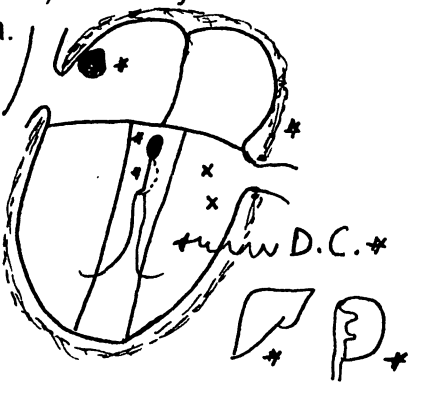
1- Start by the maintenance dose.

2- Steady State Concentration (Css) will be reached within 4 – 5 t ½.

3- Useful in Mild H.F. especially in Elderly patients.

* *Contraindications of Digitalis:*

1- Sick sinus (SAN) syndrome → Severe ↓ SAN.
2- Partial Heart Block → Complete H.B.
3- Wolff Parkinson White Syndrome (Accessory A-V bundle) → Arrhythmia.
4- Cardiac ischemia → Angina & Infarction → Arrhythmia.
5- Electro-Cardio-Version → Ventricular Fibrillation.
6- Cardiomyopathy → Not effective.
7- Constrictive pericarditis → Further ↓ C.O.P.
8- Hepatic (Digitoxin) & Renal (Digoxin) diseases.



* *Drug Interactions of Digitalis:*

A) ↓ Activity of Digitalis:

1- **↓ Absorption of Digitalis**:
   a- Anti-acids → Al & Mg.
   b- Anti-biotics → Neomycin.
   c- Anti-cholesterol → Cholestyramine.
   d- Anti-diarrhea → Pectin & Kaolin.
   e- Anti-emetic → Metoclopramide → ↑ Gastric emptying.
2- **↑ Metabolism** → Hepatic Microsomal Enzyme Inducers: Phenobarbitone, Phenytoin & Rifampicin.
3- **↑ K^+** → Retaining Diuretics e.g. Spironolactone, Triamterene & Amiloride.

B) ↑ Activity of Digitalis:

1- ↑ Absorption → Atropine & Propantheline → Delay gastric emptying.
2- ↓ K^+ → Hypokalemia e.g. Thiazide & Loop diuretics.
3- ↑ Ca^{2+} → Hypercalcemia e.g. Thiazide diuretics & I.V. Calcium injection.
4- β-Agonists → Arrhythmia.
5- β-Blockers → Heart block.
6- Verapamil & Amiodarone → ↑ Plasma level of Digitalis & ↑ Heart Block.
7- Quinidine → Displaces Digoxin from plasma proteins & ↓ its renal excretion by 50% → Double its plasma level

* *Factors That ↑ Increase Digitalis Toxicity:*

1- Drug Interactions (See Above).
2- Hpokalemia
3- Hypomagnesemia
4- Hypoxia
5- Hypercalcemia (Hyperthyroidism)
6- Acidosis
7- Extremities of age
8- Liver & Kidney disease
9- Hypothyroidism
10- Cardiac ischemia
11- Repeated Initial doses.
12- Large maintenance dose.

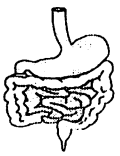
* *Toxicity of Digitalis:*

- Narrow safety margin = Low Therapeutic Index.
- Toxic plasma concentrations (Digoxin > 2 ng/ml) & (Digitoxin > 35 ng/ml)

I- Manifestations:

1- G.I.T.:

a- Early: Anorexia, nausea & Vomiting.
b- Late: Diarrhea & Abdominal cramps.



2- C.V.S.;

a- Early: Bradycardia < 60 beats / min.
b- Late; Heat block (Partial then Complete) & Arrhythmia (Atrial & Ventricular) → Extrasystoles (Pulsus bigeminus & trigiminus), tachycardia, flutter & fibrillation → Cause of Death.

3- C.N.S.: Excitation, Headache, Hallucination, Delusion, Delirium, Confusion & Convulsions.

4- Colored vision (Chromatopsia) → Yellow & Green vision.

5- Endocrine → Gynecomastia.

6- Allergy → Skin rash & Eosinophilia.

II- Treatment of Digitalis Toxicity:

1- STOP Digitalis & K^+-Depleting Diuretics.
2- Monitor plasma level of → Digitalis, K^+, Mg^{2+} & Ca^{2+}.

3- If Hypokalemia → **Potassium Chloride**
Provided No Heart block or Renal impairment.
4- If Hypercalcemia → **Sodium Edetate** → Chelation of Ca^{2+}.
5- If Hypoxia → **Oxygen**.
6- If Ventricular Arrhythmia + Heart Block → *Phenytoin* → Drug of Choice.
7- If Ventricular Arrhythmia with***out*** Heart Block → **Lidocaine**.
8- If Heart Block or Sinus Bradycardia → **Atropine**.
9- Purified Fab Fragments of **Digoxin Antibody**.
10- Oral **Cholesteramine** → ↓ Absorption of Digitoxin → # Entero-hepatic circulation.
11- ***No*** **need for**:
a- *Stomach wash*: Toxicity is due to cumulation rather than acute large dose.
b- *Dialysis*: Digitalis is highly bound to plasma & tissue proteins → Not dialyzable
c- *Electro-Cardio-Version* → Ventricular fibrillation.

Other Inotropic Agents

A) Bipyridines:

1- Amrinone:

1- ↓ Phosphodiesterase enzyme III (***↓ PDE-3***) → ↑ cAMP in Heart & B.V. → Ino-Dilator:
   a- Direct Myocardial Stimulant → +ve Inotropic Effect.
   b- Mixed V.D. (Artery & Vein) → ↓ After-load & Pre-load.
   } ↑ C.O.P.
2- ***Minimal*** Change in Heart rate & Blood pressure.
3- ***Adverse Effects***:
   a- Allergy → Fatal Thrombocytopenia & Hepatotoxicity.
   b- ↑ Myocardial O_2-consumption → Worsens Angina pectoris.
4- ***Used*** as I.V. Short term therapy in resistant heart failure to augment Digitalis.

2- Milrinone:

1- *Similar* to Amrinone ***But*** → More powerful & Less toxic.
2- ***Used*** Orally & I.V. in resistant heart failure to augment Digitalis.

B) Methyl-Xanthines

- Example: **Aminophylline** → ↓ PDE IV → ↑ CAMP → Inodilator (see CNS)

C) Sympathomimetics β_1-Agonists:

- Example: *Dopamine & Dobutamine* → ↑ Adenyl-Cyclase → ↑ cAMP (See ANS)

* Drugs Used In Treatment of Heart Failure;

1- Inotropic Agents → ↑ Contractility → ↑ C.O.P.
a- Digitalis: Digitoxin, Digoxin & Ouabain.
b- Bipyridines: Amrinone & Milrinone.
c- Methyl-Xanthines: Aminophyllline.
d- β_1-Agonists: Dopamine & Dobutamine
} Augment +ve Inotropic effect of Digitalis.

2- Diuretics → ↓ Blood volume → ↓ VR → ↓ EDV → ↓ Preload & ↓ Pulmonary congestion.
a- Thiazides e.g. Hydrochlorothiazide → Direct Art. VD → ↓ TPR → ↓ Afterload.
b- Loop e.g. Frusemide → I.V. → Veino-dilator → ↓ VR → ↓ EDV → ↓ Preload.
c- K^+-Retaining e.g. Spironolactone → # Secondary Hyperaldosteronism of H.F. &
   # Hypokalemia induced by Thiazide & Loop Diuretics

3- Vaso-Dilators:
a- Arterio-V.D. e.g. Hydralazine → ↓ T.P.R. → ↓ Afterload → ↑ S.V. & ↑ C.O.P.
b- Veno-VD eg Nitrates → ↓ VR → ↓ EDV → ↓ Preload & ↓ Pulmonary congestion.
c- Mixed VD → ↓ Preload & Afterload → ↑ COP & ↓ Congestion e.g.
   - ACE.I. (Captopril), AT_1-Antagonists (Losartan) → # Seconadry Hyperaldosteronism of HF.
   - Prazosin & Na Nitroprusside.

4- β_1-Blockers in Small Doses:
a- They protect the heart from Cardiotoxic effect induced by ↑ Increased Sympathetic activity due to H.F. → ↓ Mortality in H.F. patients.
   (↑ Sympathetic → ↑ β_1 (Cardiotoxic) + → ↑ Renin → ↑ Angiotensin & Aldosterone → Cardiotoxic → Remodeling & damage of myocardium)
b- *Example*: Metoprolol, Bisoprolol & Carvedilol (V.D. + Anti-oxidant).

Heart Failure

{Cardiac Output < Body Needs}

* Causes Of Heart Failure:

1- Excessive Pressure (Pressure Overload) e.g. Hypertension
2- Excessive Volume (Volume Overload) e.g. Mitral incompetence
3- Diseased Myocardium e.g. Myocarditis

* Precipitating Factors Of Heart Failure:

1- Respiratory infection
2- Rheumatic activity
3- Endocarditis
3- Cardiac dysrhythmias e.g. Atrial fibrillation

* Management Of Chronic (Congestive) Heat Failure (C.H.F.):

1- Treatment Of The Underlying Cause:

1- Medical treatment e.g. for Hypertension
2- Surgical treatment e.g. for valve lesions

2- Treatment Of The Precipitating Factors e.g. Respiratory Infection

3- Non-Pharmacological Measures:

1- Restriction of physical activity + Bed *rest*
2- *Weight* reduction in obese patients
3- *Diet*:
   a- Restriction of dietary salt (sodium chloride)
   b- Low caloric diet
   c- Small frequent light meals (4-6 times / day)

4- Specific Pharmacologic agents:

1- *Diuretics*: First line therapy
   a- Thiazides for mild heart failure
   b- Loop for severe heart failure
   c- K^+-Retaining diuretics e.g. Amiloride may be added to prevent Hypokalemia

2- **If** C.H.F. is **NOT** adequately controlled **ADD** *Digitalis*
   (ACE-I may be used before digitalis, added to diuretics)

3- **If** C.H.F. is **NOT** adequately controlled **ADD** *Vaso-Dilator*
   a- Arterio-Dilator e.g. Hydralazine
   b- Veno-Dilator e.g. Isosorbid dinitrate
   c- Mixed-Dilators e.g. ACE-I

4- **If** above measures **FAIL**, try other *Inotropic* Agents e.g.
   Dopamine, Dobutamine, Amrinone & Milrinone

NB) Management Of Heart Failure Associated With Atrial Fibrillation:

1- Digitalis is the drug of CHOICE
2- Digitalis does NOT cure atrial fibrillation, it may WORSEN the atrium
3- Digitalis slows A-V conduction (Prolongs Refractory Period) by BOTH Direct & Vagal effects
4- Reduces Ventricular rate → Slower, Regular & More efficient
5- Remove pulse deficit.

Management Of Acute Pulmonary edema due to Acute Left Ventricular Failure

1- The patient is in "**Sitting**" position with legs dangling

2- **Oxygen** by nasal catheter or face mask

3- **Morphine** Sulfate (10-15 mg I.V.): 5 mg I.V. repeated every 15-30 minutes
The beneficial effects of Morphine include:
   a- Veno-dilator → Venous pooling → ↓ Venous return → ↓ E.D.V. → ↓ Pre-load & ↓ Pulmonary congestion
   b- Allay anxiety → ↓ Sympathetic → ↓ TPR → ↓ After-Load
   c- Sedate respiration

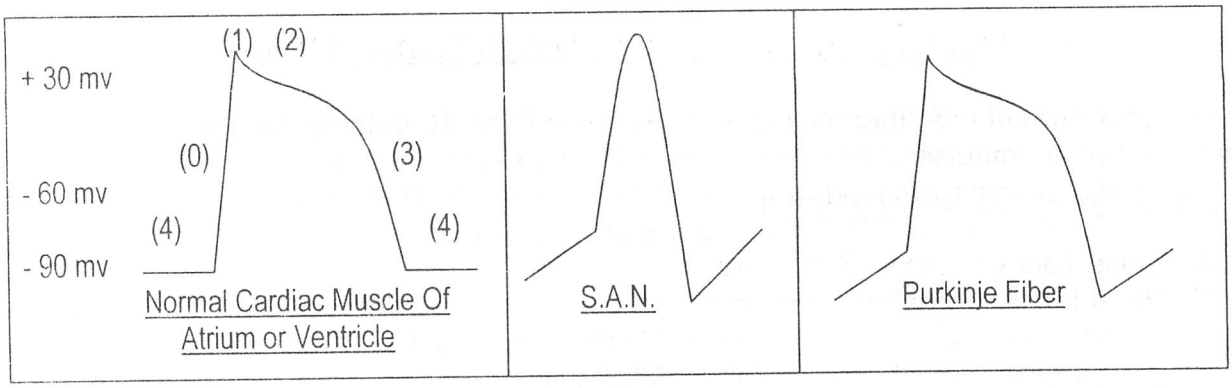
4- **Frusemide** 20-40 mg I.V. Slowly:
   a- An immediate Veno-dilator effect.
   b- A subsequent diuretic effect
   } ↓ Pre-load & Pulmonary congestion

5- **Veno-Dilators**:
   a- *Nitroglycerine* S.L. or I.V. Infusion
   b- *Na Nitroprusside* I.V. Infusion → Mixed Balanced Dilator
   } *Both Drugs → NO* = Nitrodilators → ↑ cGMP

6- **Aminophylline** 250 – 500 mg Slow I.V.
   a- +ve Inotropic effect
   b- Bronchodilator
   c- Diuretic

7- **Inotropic Agents**:
   a- Digoxin or Ouabain I.V.
   b- Dopamine or Dobutamine I.V. Infusion

8- **If above measures FAIL**:
   a- Rotating tourniquet
   b- Phlebotomy
   c- Endotracheal intubation & mechanical ventilation



* Phases Of The Action Potential:

Phase (0): Activation of Na^+ Channels → Rapid Na^+ Influx → Depolarization = Excitability & Conductivity.

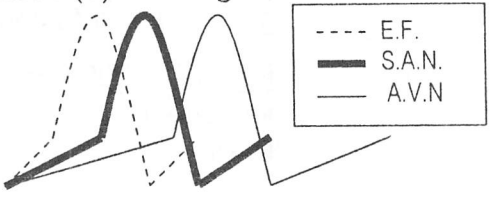
Phase (1): Inactivation of Na^+ channels. Start of K^+ Efflux.
Phase (2): Activation of Slow Ca Channels → Slow Ca Influx → Plateau.
Phase (3): Inactivation of Ca^{2+} Channels. Full activation of K^+ Channels → Rapid K^+ Efflux → Rapid Repolarization.

} Action Potential Duration (A.P.D.) = Effective Refractory Period (E.R.P.)

Phase (4): a- Normal Cardiac muscle fiber → Resting potential. Inactivated ALL channels. Activation of Na^+ / K^+ ATPase → Na/K Pump → Restore electrolyte balance.
b- S.A.N., Conductive tissue & Ectopic Focus → Slow Na^+ & Ca^{2+} Influx → Slow diastolic depolarization = Prepotentional = Automaticity.

* Drugs Blocking ion Channels:

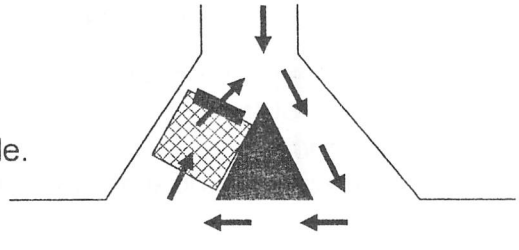
1- Block of Activated Na^+ channels → Slow Phase (0) → Slow Excitability & Conductivity.
2- Block of Inactivated Na^+ channels → Slow Phase (4) → Slow Automaticity.
3- Block of Slow Ca^{2+} Channel → Short Phase (2) of cardiac muscle fiber.
Slow Automaticity of Ectopic focus.
4- Block of K^+ channel → Delay Repolarization → Long Phase (3) → Long A.P.D. & E.R.P.



* Causes and Treatment of Arrhythmias:

A) Ectopic Focus Formation:

1- *Cause*: Any cell with Automaticity faster than S.AN.
2- *Treatment* → Slow down Automaticity of Ectopic focus by selective block of its:
a- Inactivated Na^+ channel OR
b- Block of Voltage-dependent Slow Ca^{2+} channel.



B) Re-Enterant Circus Movement:

1- *Cause*:
a- Unilateral uni-directional block of a diseased bundle.
b- Slow conduction in the diseased bundle.
c- Short Refractory period of surrounding fibers.
2- *Treatment*:
a- Block activated Na^+ Channel → ↓ Conduction & Excitability → Bi-directional block of diseased bundle.
b- Block of K^+ Channel → ↑ Effective refractory period of surrounding fibers.

Anti-Dysrhythmic = Anti-Arrhythmic Drugs

- Dysrhythmia (Arrhythmia) means any abnormality in Rate, Regularity, Origin or Conduction of an Impulse.
- Causes & Types Of Dysrhythmia:

1- S.A.N.: Sinus Tachycardia or Bradycardia
2- A.V.N.: Heart Block (Partial or Complete)
3- Single Ectopic Focus *(E.F.)*: Extrasystoles & Paroxysmal Tachycardia
4- Single Re-Enterant Circus Movement *(RECM)*: Flutter
5- Multiple Ectopic Foci or Re-Enterant Circus Movements: Fibrillation

* Classification Of Anti-Dysrythmic Drugs

I- Class I: Na^+ Channel blockers = Membrane Stabilizers

A) Group A: Block *BOTH* Na^+ & K^+ Channels:

1- Moderate block of Activated Na^+ channel → Moderate Slow of Phase (0) → Moderate slow Excitability & Conductivity
2- Block Inactivated Na^+ Channel → Slow Phase (4) → Slow Automaticity
3- Block K^+ Channel → Delay repolarization → Long Phase (3) → Long A.P.D., & E.R.P.
4- **Examples**: Quinidine, Procainamide & Disopyramide.

B) Group B:

1- Minimal Block of Activated Na^+ channel → Minimal effect on conductivity & Excitability
2- Block MAINLY Inactivated Na^+ Channel → Slow Phase (4) → Slow Automaticity
3- May Activate K^+ Channel → Rapid repolarization → Short Phase (3) → Short APD & ERP
4- **Examples**: Lidocaine & Phenytoin

C) Group C:

1- Block MAINLY Activated Na^+ Channels → Marked Slow Phase (0) → Marked Slow Excitability & Conductivity
2- **Examples**: Flecainide, Encainide & Propafenone.

2) Class II: β-Blockers e.g. Propranolol & Atenolol

3) Class III:

1- Block MAINLY K^+ Channels → Delay Repolarization → Long Phase (3) → Long APR & ERP
2- **Examples**: Amiodarone, Bretylium, Sotalol & Oxyfedrine

4) Class IV:

1- Block Voltage-dependent L-type of Ca^{2+} channels
2- S.A.N. & A.V.N. → Slow Excitability & Conductivity.
3- Ectopic Focus → Slow Automaticity
4- Normal muscle fiber → Short Phase (2)
5- **Examples**: Calcium Channel Blockers (CCB) e.g. Verapamil & Diltiazem.

Quinidine

- Class-I Group-A Anti-arrhythmic drug.
- Direct myocardial depressant
- Cinchona bark alkaloid. It is the Dextro-isomer of Quinine

* Pharmacokinetics:

1- Absorption: Orally & Parenterally
2- Distribution: 60% bound to plasma proteins. Passes B.B.B. Concentrated in Heart.
3- Excreted in urine partially unchanged. Acidification of urine → ↑ Excretion in Urine.

* Mechanism Of Action:

1- Quinidine combines with lipo-proteins of **ion channels**:

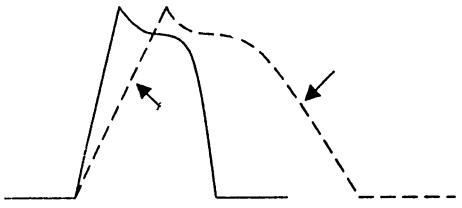
a- Moderate block of *Activated Na^+* channel → Moderate slow of phase (0) → Moderate Slow of Excitability & Conductivity

b- Block K^+ channel → Delay repolarization → Long Phase (3) → Long Action potential duration (APD) & Effective Refractory Period (ERP)

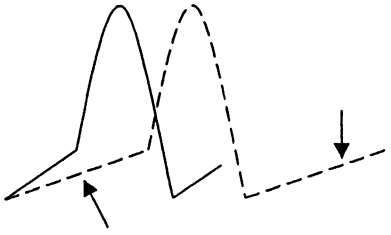
} Stop Re-Enterant Circus Movement

c- Block *Inactivated Na^+* channel → Slow Phase (4) → Slow Automaticity → Stop Ectopic focus

2- Quinidine blocks Vagal tone = **Anti-Vagal** = Vagolytic = Atropine-like effect.



——— Normal Cardiac muscle
- - - - Quinidine effect {Phases (0) & (3)}



——— Ectopic Focus
- - - - Quinidine effect {Phase(4)}

* Actions Of Quinidine:

I- Heart: Quinidine → Direct Myocardial Depressant + Atropine-like effect

1- **Contractility** → -ve Inotropic effect.
Specially in Large dose & on Diseased heart → ↓ COP

2- **Rhythmicity**:
a- Initial Tachycardia → Atropine-like effect & reflex from hypotension
b- Them Bradycardia → Direct ↓ S.A.N.

3- **Conductivity & Refractory Period**:

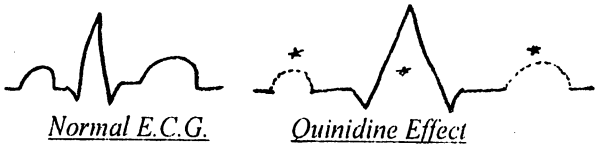
	Direct (Block Activated Na^+)	Vagolytic	Result	Refractory Period (Block K^+)
1- Atrium	↓	↓	↓↓ "BAD"	↑↑ "GOOD"
2- A-V system	↓	↑	↓ or ↑ "BAD"	↓ or ↔ or ↑
3- Ventricle	↓	- - -	↓	↑

NB) In Large dose → Direct effect takes upper hand → ↓ Conduction ALL through heart.

4- ↓ **Excitability**: Quinidine Blocks Activated Na^+ → ↓ Spread of arrhythmia.

5- ↓ **Automaticity**: Quinidine Blocks Inactivated Na^+ channel specially Ectopic Foci in Atrium.

6- **E.C.G.**:



Normal E.C.G. *Quinidine Effect*

a- Abnormal P-wave
b- Long P-R interval (specially in Large dose)
c- Long Q-R-S = Long Q-T: If *MORE* than 25% = Toxicity → Stop Quinidine
d- Abnormal T-wave.

2- *Hypotension*: Specially if injected I.V.

a- α-Block b- Veno-Dilator c- ↓ C.O.P. d- ↓ V.M.C.

3- *Local Anesthetic Action*: Block Na^+ channel → Membrane stabilizer

4- *Anti-Malarial*
5- *Anti-pyretic Analgesic*
6- *Oxytocic*
7- *Skeletal muscle relaxant*

} Similar to Quinine *BUT* Weaker

* Therapeutic Uses Of Quinidine:

Dose: 200-600 mg / 4-6 hours. Start by small test dose = One tablet

1- Atrial (Supra-Ventricular) Arrhythmias:

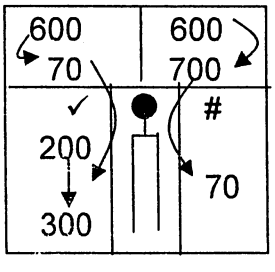
1- **Atrial Extrasystoles**.
2- **Paroxysmal Atrial (Supra-Ventricular) Tachycardia**

} Due to Ectopic Focus formation

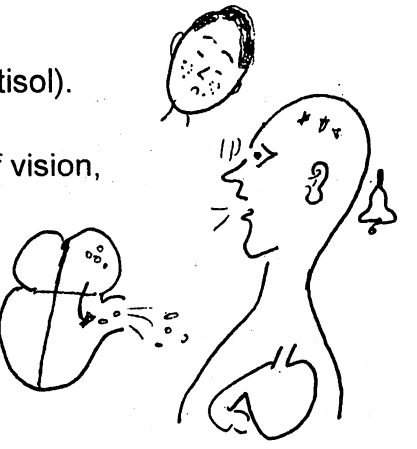
- Quinidine → ↓ Automaticity → ↓ Ectopic focus formation
  → ↓ Excitability → ↓ Spread of arrhythmia

3- **Atrial Flutter**: Due to Re-Enterant Circus Movement (R.E.C.M.)
a- *Good*: If Quinidine ↑ E.R.P. (↓ K^+) > ↓ Conductivity (↓ Na^+) → Cut RECM → Cure
b- *Bad*: If Quinidine ↓ Conductivity (↓ Na^+) > ↑ E.R.P. (↓ K^+) → Persistent RECM
c- *Bad*: If Quinidine ↑ A-V conduction by its Atropine like effect before it treats the atrium → Paradoxical Ventricular Tachycardia.
Pre-treatment by Digitalis is essential to ↓ A-V conduction by BOTH Direct & Vagal Effects → Prevent Paradoxical Ventricular Tachycardia.

4- **Recent Atrial Fibrillation (Less than 6 months)**:
a- Quinidine treats the Atrial Fibrillation whether due to E.F. or R.E.C.M.
b- Pre-treatment by Digitalis is Essential to prevent Paradoxical Ventricular Tachycardia
c- If Quinidine is used in Old A.F. (More than 6 months → Embolic Manifestations.
2- Ventricular Arrhythmias: When other measures fail.
3- Maintenance after Electro-Cardio-Version (D-C shock).

Quinidine		*Digitalis*
1- Cure Atrium		1- Worsens Atrium
2- May ↑ A-V Conduction		2- ↓ A-V conduction
3- May Worsens Ventricles → Paradoxical Ventricular Tachycardia		3- Improves Ventricles → Slower, Regular, Efficient & Eliminate Pulse Deficit.

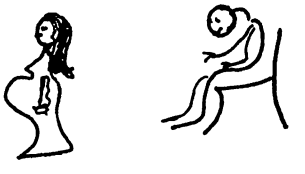
* Adverse Effects Of Quinidine:

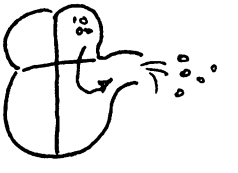


1- **Allergy** → Skin rash, asthma & Thrombocytopenia (Treat by Cortisol).
2- **Idiosyncrasy** → Hemolytic anemia.
3- ***Cinchonism:*** "Similar To Salicylism" → Headache, blurring of vision, tinnitus, deafness, nausea, vomiting & diarrhea.
4- **Embolism**:
In Old A.F. > 6 months, the auricles do NOT contract → Stagnation of blood → Thrombus formation.
Quinidine → Medical cardio-version → The auricles Start to contract again → Fragmentation & dislodgement Of the thrombus → Embolic manifestations.
NB) In Old A.F. > 6 months do NOT correct atria.
Correct ventricles by drugs ↓ A-V conduction e.g. β-Blockers & C.C.B. e.g. Verapamil
5- **Abnormal rhythm**:
a- Paradoxical ventricular tachycardia. Quinidine may ↑ A-V conduction by its atropine-like effect. Prevented by pre-treatment by Digitalis.
b- Ventricular arrhythmia: Quinidine Large Dose → Marked delay in ventricular conduction → ↑ Q-T interval > 25% → Chance for ectopic focus formation.
6- **G.I.T. disturbances** → Anorexia, nausea, vomiting & diarrhea.
7- **Severe Hypotension** specially if injected I.V. (α-Block).
8- May **fail to treat** Atrial flutter & Fibrillation if ↓ Conductivity > ↑ E.R.P.

* Contraindications Of Quinidine:

1- Allergy } - Ask for previous intake of Quinidine or quinine.
2- Idiosyncrasy } - Start by small test dose.
3- Complete Heart Block → Quinidine ↓ Idioventricular rhythm → Cardiac arrest.
4- Heart failure.
5- Hypotension.
6- Old standing Atrial Fibrillation > 6 months
7- A.F. + Subacute bacterial endocarditis } → Embolic manifestations
8- A.F. + History of embolism.
9- Digitalis induced arrhythmia.
10- Pregnancy.
11- Myasthenia gravis.





* Drug Interactions Of Quinidine:

1- **P**otassium → Potentiates Quinidine
2- **P**henobarbital → ↑ Metabolism of Quinidine
3- Quinidine → **Potentiates** the Direct V.D.
4- Quinidine → **Potentiates** Curare
5- Quinidine → **Displaces** Oral Anti-Coagulants
6- Quinidine → **Displaces** & ↓ Renal excretion of Digoxin → Doubles its plasma level.

Procainamide (Pronestyl)

- Class-I Group-A Anti-arrhythmic → Blocks Na^+ & K^+ Channels.
- Direct Myocardial Depressant.
- Related to the local anesthetic **Procaine**, *But Not* Metabolized by Pseudo-Ch.E.

*Kinetics:

1- Absorbed Orally, I.M. & I.V.
2- Distributed All-over the body and passes B.B.B.
3- *Acetylated* in liver (*Idiosyncrasy* → Slow & Rapid Acetylators) → N-Acetyl-Procainamide → Active metabolite.
4- Excreted in urine → Readjust the dose in renal insufficiency.

* Dynamics:

1- Similar to Quinidine →
   a- Class I Group-A Anti-Arrhythmic → Blocks Na^+ & K^+ Channels.
   b- Direct myocardial depressant.
   c- Atropine-like = Vagolytic action.
   BUT → *Weaker, Shorter & No α-Blocking effect compared to Quinidine.*
2- Hypotension → Especially after I.V. → Due to Ganglion blocker.
3- Local anesthetic.
4- C.N.S. excitation.

* Therapeutic Uses: Oral & Parenteral

1- Atrial Arrhythmias: Procainamide may ↑ A-V conduction by its Atropine-like effect → Paradoxical Ventricular Tachycardia. Avoid by pretreatment by *Digitalis*.
2- Ventricular Arrhythmia with***out*** Heart Block.

* Adverse Effects:

More common with Large Dose & Slow Acetylators.
1- Hypersensitivity Reactions:
   a- Skin rash & Fever.
   b- Agranulocytosis → May be Fatal.
   c- Lupus Erythematosis & Rheumatoid-like reactions.
2- C.N.S. Excitation → Psychosis & Hallucinations.
3- C.V.S. → Heart block, Heart failure, Hypotension & Ventricular arrhythmia.
4- G.I.T. disturbances.
5- Peripheral neuritis # Vitamin B-6 (Pyridoxine).

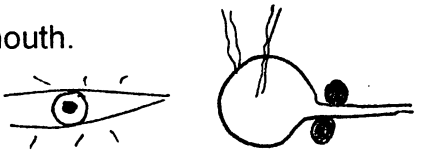
* Contraindications:

1- Hypersensitivity to Procainamide.
2- Heart block, Heart failure & Hypotension.
3- Digitalis induced Arrhythmia.

Disopyramide (Norpace)

1- **Class (I) Group (A)** Anti-Arrhythmic → Blocks Na^+ , K^+ & Ca^{2+} Channels.

2- **Similar** to Quinidine **But More**:
- a- Potent Na^+ channel blocker → Potent Local Anesthetic
- b- Potent Direct Myocardial Depressant → ↓ C.O.P. EVEN in Normal Heart.
  Contraindicated in Heart Failure & Heart Block.
- c- Potent Atropine-Like effect → Blurring of vision & Dry mouth.
  Contraindicated in Glaucoma & Enlarged prostate.



3- **Therapeutic Uses**:
- a- Atrial arrhythmia
- b- Ventricular arrhythmia with***OUT*** Heart block.
- c- Digitalis induced arrhythmia with***OUT*** Heart block.

4- May cause **V.C.** → ↑ T.P.R. → Hypertension.

Lidocaine (Xylocaine , Lignocaine)

1- **Class (I) Group (B)** Anti-Arrhythmic:

a- Blocks Inactivated Na^+ channel → Slow Phase (4) → Slow Automaticity

b- Activates K^+ channel → Rapid Repolarization → Short Phase (3) → Short APD & ERP.

2- In **Therapeutic Dose** on Normal Heart:

a- **NO** Atropine-like effect

b- **NO** Effect on S.A.N., A.V.N., Contractility or Blood pressure

3- **Local Surface anesthetic**.

4- **Therapeutic Uses** → Emergency Ventricular Arrhythmia with***OUT*** Heart Block

a- Myocardial infarction
b- Cardio- surgery or catheter
c- General anesthesia
d- Digitalis induced arrhythmia

5- **Dose**: 1-2 mg/kg I.V. Bolus, then 2-4 mg / min I.V. Infusion

6- Undergoes **Extensive Hepatic Metabolism** → Not effective Orally & Short $t_{1/2}$ = 2 Hs
Decrease its dose in Liver disease & ↓ Hepatic blood flow e.g. C.H.F. & β-Blockers.

7- **Toxicity** → C.N.S. Stimulation & Allergy

NB) Mexiletine (Mexitil) & Tocainide:
Similar to Lidocaine But → Less Metabolized → Longer $t_{1/2}$ & effective Orally & I.V.

Diphenylhydantoin (DPH, Phenytoin)

1- **Class "I" Group "B"** Anti-Arrhythmic → Blocks MAINLY Inactivated Na^+ channels.

2- **Similar** to Lidocaine ***BUT*** Weaker & May ↑ **A-V** conduction

3- **Therapeutic Uses**: Oral & Slow I.V.
- a- Anti-Arrhythmic → Ventricular arrhythmia *WITH* Heart block
  - Digitalis induced arrhythmia → Drug Of Choice
  - Myocardial infarction
  - Better *AVOIDED* in Atrial Arrhythmia → Paradoxical Ventricular Tachycardia
- b- Anti-Epileptic → Drug of Choice in Grand Mal & Partial seizures *(See C.N.S.)*.

Flecainide, Encainide, Lorcainide & Propafenone (Rytmonorm)

1- **Class "I" Group "C"** Anti-Arrhythmic
   Block Activated Na^+ channel → Slow Phase "O" → Slow Excitability & Conductivity
   Specially in Atria, Ventricles & Purkinje fibers.
2- **Propafenone** has also a β-Blocking effect
3- **E.C.G.** → Long P-R & Long Q-R-S
4- Used in **Life-threatening** Ventricular Arrhythmia & Wolf-Parkinson-White syndrome.
5- May cause Cardiac **arrest** & Sudden **Death**.

Propranolol

1- **Class "II"** Anti-Arrhythmic
   a- Small Dose → Blocks ONLY β-Adrenergic receptors
   b- Large Dose → It blocks also:
      - Na^+ channel = Class "I" Activity = Membrane stabilizer = Quinidine-like
      - Slow Ca^{2+} channels = Class "IV" activity
2- ↓ **All Cardiac properties**.
3- **Therapeutic Uses** As Anti-Arrhythmic:
   a- Sympathetic-induced arrhythmia → Use Small Dose of Propranolol
   b- Non-Sympathetic induced arrhythmia → Use Large Dose of Propranolol
   c- Particularly effective in Supra-ventricular arrhythmia
      Propranolol → ↓ A-V conduction → Protects the ventricles

Amiodarone (Cordarone)

1- **Class "III"** Anti-Arrhythmic → Blocks K^+ channel → Delay repolarization →
   Long phase (3) → Long A.P.D. & E.R.P. of whole heart.
2- Weak Na^+ channel blocker (Activated & Inactivated) → **Class "I" Activity**.
3- Weak Ca^{2+} channel blocker → **Class "IV" Activity**.
4- Weak Non-competitive α & β-blocker → Class "II" Activity.
5- Amiodarone has **ALL Classes activity** (I, II, III & IV).
6- ↓ S.A.N. & ↓ A.V.N.
7- **Therapeutic Uses**:
   a- Supraventricular & Ventricular arrhythmias.
   b- Angina pectoris → Coronary V.D., ↓ Cardiac work & ↓ O_2 needs.
8- **Adverse Effects**:
   a- C.N.S.: Headache, paresthesia, tremors & ataxia
   b- Corneal deposits.
   c- Skin deposits → Photodermatitis.
   d- Thyroid dysfunction (Amiodarone contains iodine).
   e- Pulmonary inflammation & fibrosis → May be fatal.
   f- C.V.S.: Bradycardia, heart block, heart failure & hypotension.
   g- Hepatic injury.
   i- Constipation.
   j- Drug interaction → ↓ Renal clearance of Digoxin, Quinidine, Warfarin & Theophylline.

9- **Pharmacokinetics**:
   a- Absorbed orally
   b- Extensively bound to plasma proteins
   c- Slowly metabolized → **Very Long $t_{1/2}$ = 25 - 60 days**.

Bretylium Tosylate

1- **Class "III"** Anti-Arrhythmic → Block K^+ channel → Delay repolarization → Long Phase (3) → Long A.P.D. & E.R.F. of Ventricle & NOT atria.

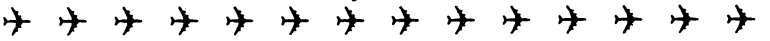
2- **Similar** to Guanethidine:
   a- Initial release of Noradrenaline → Initial sympathetic activity
   b- Then → Inhibits release of Noradrenaline → Hypotension
   c- Tricyclic Antidepressants → ↓ Uptake-1 of Bretylium → Antagonize its action

3- Used I.V. Infusion in **Life Threatening** Ventricular Arrhythmia

NB) Other Class III Anti-Arrhythmics:

1- **Ibutilide** → Blocks K^+ & Na^+ Channels → I.V. in Atrial Flutter & Fibrillation.

2- **Dofetilide** → Blocks K^+ channel → Orally to maintain sinus rhythm after ECV of A.F.



Verapamil & Diltiazem

1- **Class"IV"** Anti-arrhythmics → Block Voltage-dependent L-types of Ca^{2+} channel:
   a- Slow Automaticity of Ectopic focus
   b- ↓ S.A.N. & ↓ A.V.N. conductivity
   c- Short phase (2) in muscle fibers

2- **Therapeutic uses**:
   a- Supraventricular Arrhytmias:
      - Verapamil 5 mg Slow I.V. over 2-5 minutes is the **Choice** in treatment of P.A.T.
      - It treats the arrhythmia + ↓ A-V conduction → Protect the ventricle
   b- Ventricular arrhythmia with***OUT*** Heart Block.

3- **Contraindications**:
   a- Sick sinus syndrome
   b- Heart block
   c- Wolf Parkinson White syndrome = Presence of anomalous A-V bundle.
   d- Heart failure
   e- Hypotension
   f- With β-Blockers, Disopyramide & Digitalis toxicity

** Unclassified Other Drugs In Management of Dysrhythmia:*

1- Treatment of the **cause** e.g. Hyperthyroidism.

2- **Sedatives & tranquilizers**.

3- *Adenosine:*
   a- Stimulates A_1-receptors → Open K^+ channel, ↓ cAMP-induced Ca^{2+} influx → Hyperpolarization & ↓ Ca^{2+} dependent action potential & ↓ A.V.N..
   b- Very short duration of action
   c- 6 mg I.V. bolus in P.A.T.
   d- Adverse effects → Headache, Flush, Hypotension, Heart block & bronchospasm
   e- Its action is **Antagonized** by *Theophylline* → An Adenosine A_1-receptor blocker.
      Its action is **Potentiated** by *Dipyridamol* → ↓ Uptake of adenosine.

4- **Digitalis**:
   a- Alone in Atrial flutter & fibrillation to ↓ A-V conduction → Protect the ventricles.
   b- To prevent paradoxical ventricular tachycardia induced by Quinidine & Procainamide.
   c- Contraindications: Wolf Parkinson White Syndrome (WPW) & D.C. Cardioversion.

5- **Magnesium chloride**: Ventricular fibrillation & Digoxin toxicity

6- **Calcium chloride**: Ventricular tachycardia due to hyperkalemia.

7- *Treatment of Heart Block:*

   a- *Isoprenaline* (β NO α): 10 mg/ 8 hours S.L. or 0.1-0.25 mg S.C. or Slow I.V.

   b- Adrenaline (β + α): 0.1-0.25 mf S.C.

   c- Hydroxy-amphetamine HCl (Dual β + α): 60 mg 3-4 times /day Orally

   d- *Atropine* 0.6 mg I.V. specially in heart block due to β-blockers & Digitalis

   c- *Cortisol* 100 mg I.V. or Prednisolone 40-60 mg/day orally in Myocardial infarction
      → Suppress inflammatory reaction in the conducting system

   d- Molar Sodium Lactate I.V.

8- **Non-Pharmacologic Methods**:

   a- *Mechanical Maneuvers* → ↑ Vagal Tone → Treat P.A.T.
      - Carotid sinus massage: One side at a time for 10 seconds maximum.
      - Valsava's maneuver.
      - Eye ball pressure → NOT recommended → May cause Retinal detachment.

   b- *Electro-Cardio-Version* = *D.C. shock*:
      - Best way to correct cardiac tachy-arrhythmia.
      - Electric shock → Depolarizes the whole heart → Extinguish E.F. → S.A.N. rhythm.
      - Stop digitalis 2 days before D.C. shock, otherwise → Ventricular fibrillation.

   c- *Pacemaker* in severe brady-arrhythmia

NB) Vasodilators in Treatment of Vascular Insufficiency:

1- **α-Adrenoceptor Blockers** e.g. Phentolamine

2- **β_2-Adrenoceptor Agonists** e.g. Nylidrine & Isoxsuprine

3- **Parasympathomimetics** e.g. Methacholine

4- **Papaverine**: A Benzylisoquinoline alkaloid of opium

5- **Nicotinic acid** (Also Hypocholesterolemic) & **Nicotinyl Alcohol** (Ronicol)

6- **Adnenosine Triphosphate** (ATP) I.M.

7- **Piribedil** (Trivastal) → Dopamine agonist.

8- *Pentoxyfylline* (Trental) → Xanthine derivative.
   a- V.D.
   b-Improves RBCs flexibility
   c- ↓ Fibrinogen → ↓ Blood viscosity
   d- ↓ Platelet aggregation

S H O C K

A state of severe and generalized reduction in tissue perfusion by O_2 & nutrients → Reversible then irreversible cell injury.

* Clinical Manifestations :

1- Mean arterial Bl.p. < 60 mmHg. 2- Low COP. 3- Tachycardia.
4- Urine output < 20 ml/hour. 5- Anxiety, confusion, pallor, sweating & nausea.
6- Metabolic acidosis due to elevated blood lactate by anaerobic glycolysis.

* Aim of Treatment :

1-Treatment of the cause.
2-Replacement of any lost fluid from the circulation.
3-Maintenance of diastolic pressure and perfusion of vital organs.

* Precautions :

1- Avoid sedatives → ↓ VMC.
2- Avoid Alcohol → ↓ CNS & Cutaneous VD.
3- Avoid Over Heating → Cutaneous VD.
4- Avoid Head-Down position → Abdominal viscera press the diaphragm → Difficult breathing. Better raise the foot of the bed 15-30 cm → ↑ VR → ↑ COP → ↑ Cerebral blood flow.

* Types of Shock :

1- Primary or Neurogenic. 2- Secondary or Hypovolemic or Oligemic. 3- Cardiogenic.
4- Septic or Hyperdynamic. 5- Anaphylactic.

I- Primary (Neurogenic) Shock :

A) Etiology :

- Severe pain or anxiety → Release of mediators e.g. histamine & kinins → VD and ↑ capillary permeability → ↓ VR & ↓ COP.
- Spinal Anesthesia & Spinal trauma → ↓ Sympathetic activity → VD → Spinal shock.

B) Treatment :

1-**Rest** in recumbent position. Raise the foot of the bed by 15-30 cm.

2-Narcotic Analgesics : **Morphine** HCl 5 mg IV/15-30 min max 15 mg → ↓ Pain & anxiety.

3-**Sympathomimetic** : Ephedrine 25 mg IV or Dopamine (Moderate – Large dose) 10-20 ug/kg/min IV infusion → ↑ Bl.p. in spinal shock.

II- Secondary (Hypovolemic & Oligemic) Shock :

A) Etiology :

1-Rapid loss of large volume of blood (Hge), serum (Burn) & fluids (vomiting and diarrhea)
2-A healthy adult can compensate for the sudden loss of 10% of total blood volume.
If 20-25% of blood is rapidly lost → ↓ VR → ↓ Preload → ↓ COP → Shock.

B) Treatment :

1- *Volume replacement* → Improve C.O.P. :
a-Blood transfusion, in hemorrhage.
b-Plasma or plasma expander if compatible blood is not available.
c-Fresh plasma, in specific coagulation defects.
d-Crystalloids (Saline & glucose 5%), but they are NOT retained in circulation for adequate time.

2-**Dopamine** (Small – Moderate Dose) 2-10 ug/kg/min → +ve Inotropic & V.D. of Renal, coronary & mesenteric.

3-**Phenoxybenzamine** → α-blocker → VD of vital organs & ↓ excess ADH (vasopressin) secretion → Prevent the change of reversible to irreversible shock.

N.B.) Replacement of lost volume is essential before dopamine and phenoxybenzamine administration.

4- **Corticosteroids** specially those with salt retaining activity.

III- Cardiogenic Shock :

A) Etiology: Myocardial infarction, myocarditis, pulmonary embolism or arrhythmia.

B) Treatment: *See clinical of Myocardial Infarction*

1-**Oxygen**.

2-**Inotropic Agents** :
a-Dopamine (10-15 ug/kg/min) → Dual stimulation of β_1-adrenoceptors → +ve Inotropic.
Avoid large dose of dopamine → α-stimulation → VC → ↑ After load.
b-Dobutamine (2.5-10 ug/kg/min) → Direct & selective β_1-agonist → +ve Inotropic.

3-**V.D.** : Sodium Nitroprusside (0.5-10 ug/kg/min) → Mixed balanced VD → ↓ Both after & pre-load → Improve cardiac performance.

4-VC are better avoided.

IV- Septic Shock :

A) Etiology: Endotoxins of gram +ve & -ve bacteria → ↓ Heart & mal-distribution of blood → Distributive shock.

B) Treatment:

1-**Culture and sensitivity** test.

2-Full doses of specific **antimicrobials**.

3-**Oxygen** → Improve pulmonary perfusion.

4-**Plasma** transfusion → ↑ Intravascular volume.

5-**Dopamine or Dobutamine** infusion.

6-**Adrenal steroids** : Dexamethasone 2-6 mg/kg IV.

7-**Other agents** :
a-Monoclonal antibodies against bacterial endotoxins.,
b-Antagonists of endogenous cytokines.
c-Naloxone : Endotoxins → Release endorphins → Hypothalamus → ↓ Sympathetic.

V- Anaphylactic Shock :

A) Etiology: Allergic reaction to parenterally administered antigens e.g. penicillins.

B) Treatment:

1-**Adrenaline** 0.5 - 1 mg IM, repeated in 5-10 min if necessary.

2-**Antihistaminics** (H_1-blockers) : Diphenhydramine HCl 10-20 mg IV.

3-**Steroids**: Hydrocortisone Na succinate (100-250 mg IV) or prednisolone (50-100 mg IV)
a-Formation of lipocortin → ↓ PLA_2 enzyme → ↓ Arachidonate (PGs & LTs) & PAF.
b-↓ Formation of other cytokines e.g. ILs, TNF & GM-CSF.
c-↓ Capillary permeability → ↓ Exudation of inflammatory cells & maintain plasma membrane integrity.
d-Stabilization of lysosomal membrane → ↓ Release of cell damaging enzymes.
e-Immunosuppressive : ↓ Ab formation, ↓ Ag/Ab reaction & stabilizes mast cells.
f-Myocardial stimulant.
g-Those with salt retaining activity → ↑ Blood volume.

4-**Aminophylline** 250-500 mg in 10-20 ml saline slow IV if there is bronchospasm.

Blood

* Blood Coagulation:

Prothrombin —(Thromboplastins + Platelets + Ca^{2+})→ Thrombin → Fibrinogen → Fibrin

Control Of Bleeding

A) Local Hemostatics = Styptics:

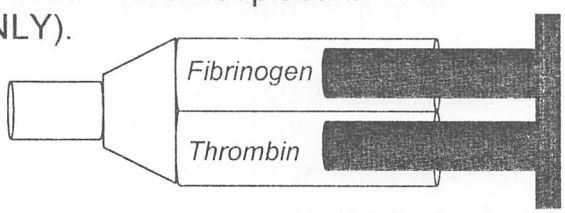
1- *Physical Methods*: Pressure, Cold & Cautary.

2- *Vaso-constrictors*: Adrenaline nasal pack in Epistaxis.

3- *Astringents*: Tannic acid & Alum → Precipitate blood proteins.

4- *If due to Varicose veins e.g. Esophageal varices* → Use *Sclerosing Agents*:
   a- *Examples*: Ethanolamine oleate & Na^+ Tetradecyl Sulfate.
   b- Irritant substances → Injected in varicose veins → Thrombosis & inflammation → Fibrosis & obliteration.

5- *Local Coagulants*:
   a- *Thromboplastin*:
      - Coagulen (Topical & I.M.) : Mammalian tissue Thromboplastin.
      - Russell's Viper Venom (Topical use ONLY).
   b- *Thrombin*.
   c- Fibrin Glue: Fibrinogen + Thrombin
   d- *Human fibrin foam*.
   e- *Absorbable Gelatin Sponge*.
   f- *Oxycel (Oxidized Cellulose)*:
      - Surgical tissue with sticky surface → Mechanical block & clot formation.
      - Not absorbed → Not left in wounds.



B) Systemic Coagulants:

1- *Fresh blood transfusion* → Restore volume & supply coagulation factors.

2- *If due to capillary fragility*:
   a- Vitamin C (Ascorbic acid) + Vitamin P (Rutin) → Treat Scurvy.
   b- Ethamsylate *(dicynone)* Orally & injection.

3- *If due to Hemophilia*:
   a- Anti-hemophilic globulin (Factor VIII)
   b- Arginin Vasopressin & Danazol → ↑ Factor VIII synthesis.

4- *If due to Thrombolytic (Fibrinolytic) therapy* → Use Anti-Fibrinolytics e.g. Aminocaproic acid & Tranexamic acid.

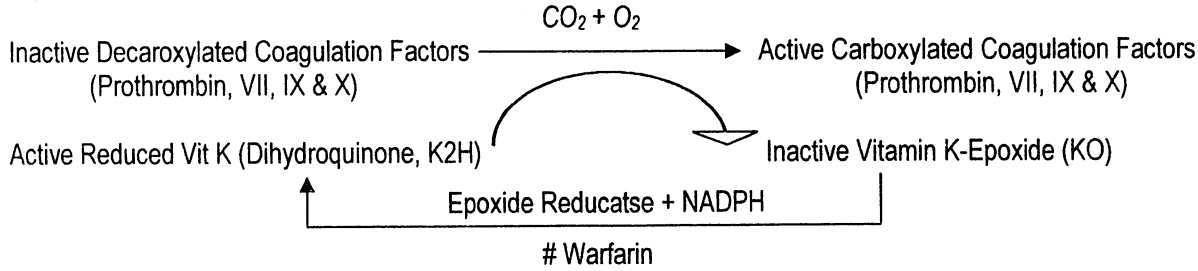
5- *If due to Anticoagulant therapy*:
   a- *If Heparin$^-$ → Use Protamine$^+$ sulfate* → Chemical neutralization.
   b- *If Oral Anticoagulant e.g. Warfarin → Use Vitamin K (Phytomenadione).*

* Vitamin K:

1- Quinone derivative.

2- Vitamin K (Quinone, K) —(Vit- K Reductase)→ Active Reduced Form (Dihydroquinone, K2H).

2- Essential for hepatic synthesis of activated (Carboxylated) coagulation factors II (Prothrombin), VII, IX & X.



3- *Therapeutic Uses*: Hemorrhage due to *Hypoprothrombinemia* →
- a- ↓ Synthesis of Vit K by intestinal flora → Oral broad-spectrum antibiotics.
- b- ↓ Absorption of Vit K → Liquid paraffin, Obstructive jaundice & Mal-absorption.
- c- ↓ Hepatic utilization of Vit K → Hepato-cellular damage.
- d- Drug induced hypoprothrombinemia → Oral anticoagulants & Salicylates.

4- *Preparations of Vitamin K*:
- a- Phytomenadione (Vit K-1):
  - Natural, of Plant origin.
  - Fat soluble → Needs bile for absorption.
- b- Menaquinone (Vit K-2):
  - Natural, synthesized by intestinal flora.
  - Fat soluble → Needs bile for absorption.
- c- Menadione (Vit K-3): Synthetic , Fat soluble.
- d- Menadiol Na Diphosphate (Vit K-4): Synthetic , Water soluble
  → No need for bile. Displaces bilirubin in neonates → Jaundice & Kernictrus.

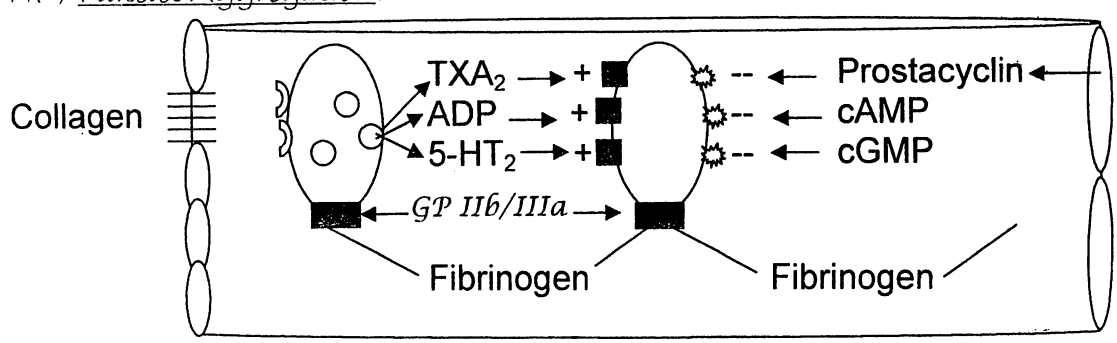
Control Of Thrombo-Embolic Disorders

1- Inhibitors of Platelet Aggregation → Prevent thrombus formation.

2- Thrombolytics (Fibrinolytics) → Dissolve already formed thrombus.

3- Anti-coagulants → Prevent thrombus formation & extension of present thrombi.

NB) Platelet Aggregation:



NB) Physiology of Platelet Aggregation:

↑ Platelet Aggregation	↓ Platelet Aggregation
1- Thromboxane A_2 (TXA_2)	1- Prostacyclin (PGI_2)
2- Adenosine Di-Phosphate (ADP)	2- cAMP
3- Serotonin 5-HT_2 receptors	3- cGMP
4- GP IIb/IIIa receptors	

Anti-Platelet Agents

- Agents used to inhibit platelet aggregation.
- Prophylaxis of intravascular thrombosis → ↓ Arterial thrombosis MAINLY.

1- ↓ Thromboxane A_2 - Synthesis:

a- Aspirin in small dose (75 -150 mg) → Acetyltaion → Selective & irreversible inhibition of platelet thromboxane synthetase enzyme.

b- Dazoxiben → Selective inhibitor of platelet thromboxane synthetase enzyme.

c- Sulphinpyrazone → Uricosuric agent & ↓ C.O.X. → ↓ PG synthesis.

d- Fish oil (Omega 3-marine triglycerides) → Eicosapentaenoic acid → Abnormal PGs & LTs → TXA_3 (less platelet activator) & PGI_3 (Powerful antiplatelet).

2- ADP-Receptor Blockers:

a- *Examples*: Ticlopidine *(Ticlid 250 mg)* & Clopidogrel *(Plavix 75 mg)*

b- *Adverse effects* → Expensive, Slow onset (3-7 days), Diarrhea, Bleeding & Neutropenia.

3- Selective 5-HT_2 antagonist → Ketanserin → ↓ Platelet aggregation + VD.

4- Glycoprotein (GP) IIb / IIIa Receptor Blockers:

a- Abciximab I.V. → GP IIb/IIIa monoclonal antibody.

b- Tirofiban *(Aggrastat)* → Reversible GP IIb / IIIa receptor antagonist.

4- Prostacyclin (PGI_2) analogues → Epoprostenol & Iloprost → I.V.

5- ↑ cAMP:

a- Dipyridamol → Coronary VD & ↓ Phosphodiesterase enzyme (PDE) → ↑ cAMP.

b- Pentoxifylline: Methylxanthine derivative → ↓ P.D.E. → ↑ cAMP:

- ↓ Platelet aggregation.
- Restores flexibility of RBCs membrane.
- ↓ Fibrinogen in blood → ↓ Viscosity of blood.
- Useful in treatment of intermittent claudication.

6- ↑ cGMP: Nitrates & Nitroprusside → Release Nitric Oxide → ↑ Soluble Guanylate Cyclsae Enzyme → ↑ cGMP → ↓ Platelet Aggregation & V.D.

7- Miscellaneous:

a- β-Blockers.

b- Calcium channel blockers.

c- Clofibrate → Hypocholesterolemic agent.

d- dextran 70 & 75.

Thrombolytics & Fibrinolytics

Streptokinase → + + Proactivator → Plasminogen Activator

Plasminogen (Profibrinolysin) —(++ Urokinase)→ Plasmin (Fibrinolysin) → Lysis of Fibrin.

- Agents use to lyse recently (< 72 hours) form thrombi & emboli.
- Injected I.V., intraarterial & intracoronary.
- Useful in coronary thrombosis , multiple pulmonary emboli & deep venous thrombosis.

1- Streptokinase:

a- Obtained from Hemolytic Streptococci → Antigenic.
b- Combines with Pro-activator → Complex → Activation of Plasminogen.
c- 1.5 million units in 200 ml saline I.V. infusion, single dose.
d- Anistreplase → Plasminogen-Streptokinase Complex

2- Urokinase:

- Obtained from human urine → Not antigenic. Direct activator of plasminogen.

3- Tissue Plasminogen Activator (t-PA, Alteplase, Actilyse):

a- Prepared by recombinant DNA technology → Not antigenic BUT Expensive.
b- Selective activation of plasminogen bound to fibrin & not circulating plasminogen → More effective, No systemic fibrinolysis & Rapid acting.
c- 10 mg I.V. bolus then 50 mg over an hour then 40 mg over 2 hours.

N.B.) Anti-Thrombolytics (Anti-Fibrinolysins):

1- Examples: Aminocaproic acid & Tranexamic acid
2- Mechanism: Competitive antagonists of plasminogen activators.
3- Used to treat hemorrhage induced by over dose of thrombolytics.

Anti-Coagulants

1- Drugs That REMOVE Ionic Calcium:

a- By Precipitation: Na^+ or K^+ Oxalate → Used In-Vitro Only e.g. Test tubes.
b- By deionization → Combine with Calcium without precipitation → Chelation → Na^+ Citrate 3.8% & Na^+ Edetate → Used In-Vitro Only e.g. Blood transfusion.

2- Oral Anti-Coagulants: Effective In-Vivo Only.

a- Coumarines: Warfarin & Dicoumarol.
b- Indanediones: Phenindione & Diphenadione.

3- Injectable Anti-Coagulants:

a- Thrombin Inhibitors = Anti-Thrombin:
- Direct Anti-Thrombin: Hirudin & Hirulog.
- Indirect Anti-Thrombin: Heparins (High & Low Molecular Weight Heparins)

b- Thrombin-Like → Fibrinogen Depletors → Ancrod.

Heparin

* Source:

1- Present naturally with Histamine in Mast cells & Basophils in lung, liver & intestine.
2- Obtained from bovine lung & porcine intestinal mucosa.

* Chemistry:

1- Sulfated muco-polysaccharide.
2- Strong acid → Carries strong electronegative charges → Poly-anionic.

* Pharmacokinetics:

1- *Not* absorbed orally. Used *either* I.V. or S.C. *NEVER I.M.* → Hematoma.
2- Distributed Intra-vascularly.
Dose *NOT* pass B.B.B. or Placental Barriers → Allowed in pregnancy.
95% Bound to plasma proteins.
3- Partially metabolized by *Hepatic Heparinase* enzyme → Uroheparin.
4- Excreted in urine partially as Heparin (20%) & *Mainly* as Uroheparin (80%).
Not excreted in Milk → Does *Not* Affect suckling baby.
5- I.V. → Immediate onset of action & Short duration (4 - 6 hours).

* Pharmacodynamics:

A) Anti-coagulant BOTH In-Vivo & In-Vitro:

1- Heparin acts on *Preformed* activated coagulation factors e.g. Thrombin.
2- Its electronegative charges are essential for its activity.
3- *Mechanism of Action*:
a- Combines to & Activates *Anti-Thrombin III* (Heparin cofactor or Protease inhibitor) → Neutralization of activated factors II_a (Thrombin), IX_a, ***X_a (Mainly)*** & XII_a.
b- Activation of Heparin cofactor II → Specific Anti-thrombin.
c- Heparin is antagonized by platelet factor IV.

B) Lipemia Clearing effect via activation of Lipoprotein lipase enzyme.

* Doses of Heparin:

1- 1 mg Heparin = 100 Units.
2- *Routes of Administration*:
a- I.V. bolus injection: 10'000 U initially then 5000-10'000 u / 4 – 6 Hours.
b- I.V. Infusion: 10'000 U initially *then* 1000-1500 U (10-15 U/kg) / Hour.
c- Deep S.C. (Abdominal wall) small dose Heparin: 5000 / 8 - 12 hours.
3- *Control of Dose*:
a- Coagulation time = Whole Blood Clotting Time (WBCT) = Normally 4-8 minutes → Prolonged 2 – 2.5 times.
b- Activated Partial Thromboplastin Time (APTT) = Normally 26 – 33 seconds → Prolonged 2 – 2.5 times.

* *Heparin Antagonists:*

a- *Protamine Sulfate* → Strong Base → Chemical Neutralization of Heparin.
1 mg Protamine SO_4 1% solution for each 1 mg (100 U) Heparin.
Excess Protamine SO_4 → Bleeding.
b- Fresh blood transfusion.

* *Adverse Effects of Heparin:*

1- Hemorrhage.
2- Hypersensitivity.
3- Prolonged use of full dose → Transient Alopecia & Osteoporosis.
4- *Thrombocytopenia*, of 2 types:
a- Mild & transient due to heparin-induced platelet aggregation.
b- Severe & persistent due to heparin-induced Anti-platelet Antibodies.

N.B.) Low Molecular Weight Heparin (LMWH):

1- Examples: ***Enoxaparin*** *(Clexane)*, Dalteparin *(Fragmin)* & Rivaparin
2- Small fraction of unfractionated heparin (MW = 5000 – 8000) → High affinity to *Anti-Thrombin III* → Strong Inhibitor of activated factor X_a.
Minimal effect on platelet aggregation or lipo-protein lipase activity.
3- Advantages:
a- Minimal bleeding tendency .
b- Long t ½ → S.C. or I.V. od or bid.
c- Easy calculation of dose → No need for laboratory monitoring.

N.B.) Danaparoid:

1- Non-heparin anticoagulant isolated from porcine intestinal mucosa.
2- Used I.V. or S.C. in patients with Heparin-induced allergy or thrombocytopenia.

N.B.) Hirudin & Hirulog:

1- Obtained from Medicinal leech.
Now synthesized by rDNA technology → **Lepirudin** I.V. infusion.
2- Direct & selective *Thrombin inhibitors*.
3- *Not* dependent on Anti-thrombin III & *Not* antagonized by platelet factor.
4- Useful in patients allergic to heparin or develop thrombocytopenia.

N.B.) Ancrod:

1-An enzyme of Ancrod snake venom.
2- Thrombin like *But* → Abnormal fibrin → Rapid fibrinolysis & uptake by R.E.S.
→ Depletion of Fibrinogen.
3- Side effects → Hemorrhage & Hypersensitivity.
4- Anti-dote: Fibrinogen & Anti-venom.

Warfarin sodium (Marevan, Hemofarin)

* *Nature:* Synthetic oral anticoagulant. Coumarin derivative.

* *Pharmacokinetics:*

1- Well absorbed orally → 100% Bioavailability.
2- Distributed All-over the body and passes BBB & Placental barrier.
3- Highly (99%) bound to plasma albumin.
4- Metabolized (hydroxylated) SLOWLY by hepatic microsomal enzyme.
5- Excreted in urine *But Not* milk.
6- Onset of action: Delayed after 1-2 days. Duration of action : Long for 5-7 days.

* *Pharmacodynamics :*

1- *Anticoagulant* In-Vivo Only :
   a- l-isomer (S-form) is 4 times Stronger than the d-isomer (R-form).
   b- ↓ Vit-K Epoxide Reductase enzyme → ↓ Reactivation of Vit K.
   c- ↓ Vit K-dependent hepatic synthesis of activated (carboxylated) thromboplastins → Prothrombin (factor II) & factors VII, IX & X.
2- *Rodenticide*.

* *Dosage & Its Control :*

1- Initial dose 5-10 mg/day for 2 day orally, then maintenance dose 2-10 mg/day orally according to prothrombin time.
2- *Control of Dose*:
   a- Prothrombin time (normally 12-15 seconds) → Prolonged 2-3 times
      = International Normalized Ratio (INR) = 2-3.
      INR = Prothrombin time of patient / Standard prothrombin time.
   b- Prothrombin activity → Reduced to 25% of normal.

* *Antagonists :*

1- Phytomenadione (Vit K_1): 50 – 100 mg IV.
2- Fresh blood transfusion.

* *Side Effects & Toxicity :*

1- Hemorrhage.
2- Hypersensitivity.
3- G.I.T. disturbances.
4- Teratogenicity.
5- Sudden Stop → Rebound thrombo-embolic manifestations.

* *Other Oral Anti-Coagulants: Similar to Warfarin.*

1- *Dicoumarol:*

1- Synthetic Coumarin derivative, also present in plants (spoiled Sweet clover).
2- Kinetics & dynamics similar to Warfarin *BUT Weaker* by 1 : 40.
3- More toxic than Warfarin → NOT suitable for long term therapy.

2- *Indandione Derivatives:*

- Phenindione *(Dindivan)* & Diphenadione → Similar to warfarin *But* More toxic.

* Drug Interactions of Oral Anticoagulants:

A) Drugs that ↑ Potency of Oral Anticoagulants:

Decrease the dose of oral anticoagulants, otherwise → Bleeding (treat by Vit K).

1- **↓ Vit K Synthesis by intestinal Flora**: Oral broad-spectrum Antimicrobials.
2- **↓ Vit K Absorption**: Liquid paraffin.
3- **↓ Reduction of Vit K Epoxide**: some Cephalosporins e.g. Cefoperazone.
4- **Hepatic Microsomal Enzyme Inhibitors**: Cimetidine, Clofibrate, Chloramphenicol & Allopurinol.
5- **Displacement from Plasma Protein Binding Sites**: Phenylbutazone, Sulfa,
   - Aspirin (it also ↓ platelet aggregation & produces hypoprothrombinemia),
   - Clofibrate (it also ↓ platelet aggregation & enzyme inhibitor).
6- **↓ Platelet Aggregation & Platelet function**: Aspirin & Moxalactam.

B) Drugs that ↓ Potency of Oral Anticoagulants :

Increase the dose of oral anticoagulant, otherwise → Thrombosis.

1- **Vit K**: Green leafy vegetables.
2- **↓ Absorption of Oral Anticoagulants**: Cholestyramine & Al $(OH)_3$ gel.
3- **Hepatic Microsomal Enzyme Inducers**: Phenobarbitone, Phenytoin, Rifampicin & Tobacco smoking.
4- **Estrogens & Oral Contraceptives** → ↑ Coagulation factors & ↓ Antithrombin III.

* Use of Anti-Coagulants:

A) Schedule of Therapy:

1- Start by *Both* Heparin & Warfarin.
2- Stop Heparin once Warfarin prolongs prothrombin time usually 2-4 days.
3- For long term therapy use Warfarin.
4- During Pregnancy use Heparin. Warfarin is *Contraindicated* → Teratogenic & Neonatal hemorrhage during labor → Intra-cranial hemorrhage → Fatal.

B) Indications of Anti-Coagulants:

1- Prophylaxis of Thrombo-embolic diseases & prevent extension of already present thrombus:
   a- More effective in Venous rather than Arterial *(Platelet aggregation)* thrombosis
   b- Cerebral, central retinal, pulmonary, coronary & deep venous thromboses.
   c- Coronary angioplasty & stent replacement.
   d- Long standing Atrial fibrillation.
   e- Disseminated intravascular coagulation after massive tissue damage.
   f- During & after major surgery → Use Deep S.C. Small Dose Heparin.
2- Artificial kidney & Cardio-pulmonary by-pass.
3- During Blood transfusion.
4- Heparin as lipemia clearing agent.
5- Warfarin as Rodenticide.

* Contra-indications of Anti-Coagulants:

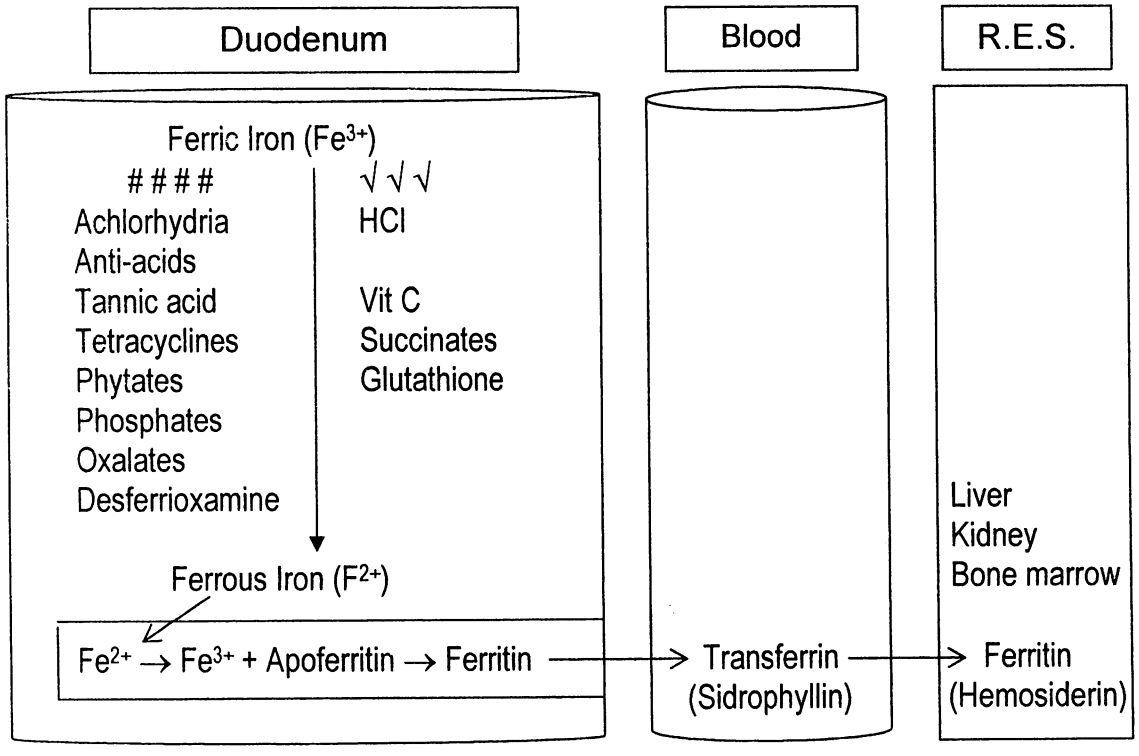
1- Hypersensitivity reaction to Anti-coagulants.
2- Hemorrhagic tendency e.g. Hemophillia & thrombocytopenia.
3- During or after Surgery in brain, spinal cord or eye → Closed spaces.
4- Head injury & Intracranial hemorrhage.
5- Severe hypertension & Bacterial endocarditis.
6- Active tuberculosis.
7- G.I.T. ulcers e.g. peptic ulcer.
8- Advanced liver & kidney diseases, and visceral carcinoma.
9- Threatened abortion.
10- Warfarin during pregnancy.

	Heparin	Warfarin
1- Source:	Natural	Synthetic
2- Chemistry:	Sulfated muco-polysaccharid, Polyanionic → Strong acid.	Coumarin derivative
3- Kinetics:		
a- Absorption:	Parenteral *Not* oral.	Orally
b- Distribution:	*Not* B.B.B. or Placental barrier.	Passes B.B.B. & Placental barrier
c- Binding:	95%	99%
d- Metabolism:	Rapid hepatic Heparinase	Slow by Hydroxylase
e- Excretion:	Renal → 20% Heparin + 80% Uroheparin, *But Not* Milk	Slow renal, *But* not milk.
f- Onset:	I.V. → Immediate	Delayed 1- 2 days
g- Duration:	Short 4 – 6 hours	Long 4 – 7 days
4- Dynamics:	1- Anti-coagulant In-Vivo & In-Vitro a- ↑ Anti-Thrombin III b- ↑ Heparin cofactor II c- Direct Anti-Thrombin 2- Lipemia Clearing Effect	1- Anti-coagulant In-Vivo *Only*: a- ↓ Vit-K Epoxide reductase → ↓ Reactivation of Vit K → Activation of Thrombin & Factors VII, IX & X. b- Rodenticide.
5- Control of Dose:	Coagulation time (WBCT) & P.T.T.	Prothrombin time (INR) & activity.
6- Antidote:	Protamine sulfate	Vit K-1
7- Toxicity:	1- Hemorrhage 2- Hypersensitivity 3- Alopecia & Osteoporosis 4- Thrombocytopenia	1- Hemorrhage 2- Hypersensitivity 3- GIT disturbances 4- Teratogenic 5- Sudden stop → Rebound
8- Indications	See Before	
9- Contraindications		

Anti-Anemic Drugs

I- Deficiency Anemias

A) Iron Deficiency Anemia (Microcytic Hypochromic)



* Physiological Considerations About Iron:

1- Daily requirements of iron in Males (1 mg) & Females (2-3 mg).
Requirements ↑ during Anemia, Pregnancy & Growing children.

2- Only 10% of ingested iron is *Actively* absorbed mainly from *Duodenum*.
Anemic patients can absorb up to 20% of ingested iron.

3- Iron is absorbed in the *Ferrous* (Fe^{2+}) state:
a- ↑ Absorption: Gastric HCl, Ascorbic acid (Vit C), Succinic acid & Glutathione.
b- ↓ Absorption: Achlorhydria, Antacids, Tannic acid, Tetracyclines, Phytates, Phosphates, Oxalates & *Desferrioxamine*.

4- In duodenum $Fe^{2+} \rightarrow Fe+^{3}$ + Apoferritin → Ferritin.

5- In blood iron is carried by Transferrin (Sidrophilin), a Glycoprotien β_1-globulin.

6- Iron is stored in Reticulo-endothelial system (RES) e.g. Liver, kidney & bone marrow as Ferritin (Hemosiderin).

7- Saturation of tissue stores → Saturation of blood transferrin → Saturation of mucosal ferritin → *Mucosal Block* → No more absorption of oral iron.

8- Iron is *excreted* mainly via desquamation of epithelium of Skin & GIT mucosa.

* *Iron Preparations:*

The speed of response (blood picture & Hb%) is the same whether is was used orally or parenterally. Parenteral iron produces more rapid filling of stores.

A) Oral Iron Preparations:

1- Ferrous sulfate 200 – 300 mg tds after meals → *Most Irritant*
2- Ferrous Gluconate 600 mg tds after meals
3- Ferrous Fumarate 200 mg tds after meals
4- Iron Choline Citrate solution or tablets → *Least irritant* → Suitable for children.

B) Parenteral Iron Preparations:

1- Iron Dextran *(Imferon)* 50 mg/ml I.V. & I.M.
2- Iron Sorbitol Citric Acid Complex *(Jectofer)* 50 mg/ml I.M.

* *Adverse Effects & Toxicity of Iron:*

A) Iron is ***contraindicated*** in hemolytic anemia → Deposition of iron in tissues → *Hemosiderosis*.

B) Oral Iron:

1- Oral solution → Washable black discoloration of teeth.
2- G.I.T. Irritation → Nausea & vomiting:
   a- Maximum with Ferrous sulfate.
   b- Minimum with Iron choline citrate → Preferred in children.
3- Constipation (astringent effect) or Diarrhea (Irritant effect).
4- Acute Oral Iron *Poisoning*:
   a- GIT → Abdominal pain, vomiting, hematemesis & black or bloody diarrhea.
   b- Systemic → Acidosis, Shock & Death especially in children.
   c- *Treatment of Poisoning*:
      - Ingest Raw egg + Milk
      - Stomach wash by $NaHCO_3$ or better *Desferrioxamin* (Desferal) 5-10 g in 100 ml saline via gastric tube.
      - *Desferrioxamine* (Desferal) 2 g / 12 hours I.M. of I.V. pump.

C) Parenteral Iron:

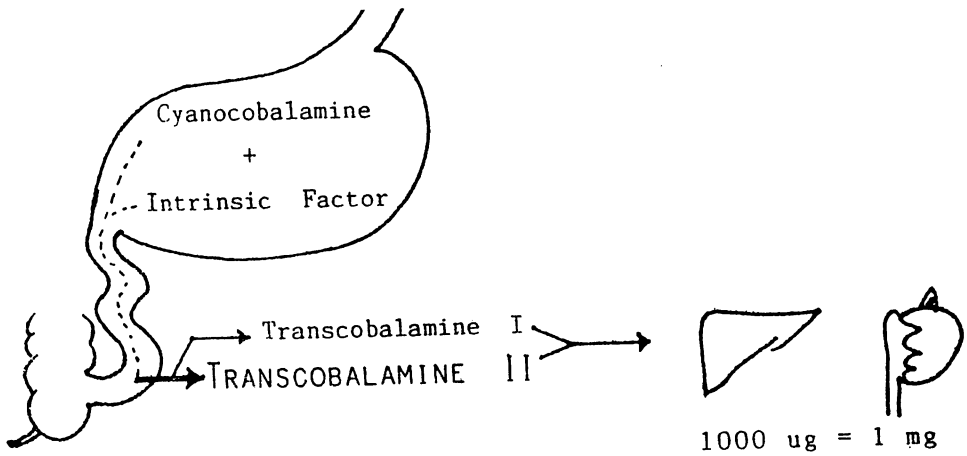
1- Local → Pain, pigmentation & inflammation.
2- Systemic → Headache, encephalopathy, convulsions & fainting.
   Tachycardia, hypotension, hemolysis & bronchospasm
   Muscle & joint pains, and skin rash.
3- Treatment of Toxicity: *Desferrioxamine* (Desferal) + Symptomatic treatment.

B) Macrocytic Hyperchromic Anemias

1- Pernicious anemia → Macrocytic hyperchromic anemia + GIT & Nerve affection.
Treat by Cyanocobalamine (Vit B-12) ± Folic acid. ***Never Folic acid alone***.

2- Megaloplastic anemia → Macrocytic hyperchromic anemia without GIT or Nerve.
Treat by Folic acid.

1- Cyanocobalamine (Vit B-12)



* Physiological Considerations About Cyanocobalamine:

1- The stomach secretion *Intrinsic factor* → Combines with Cyanocobalamine.
2- In Terminal Ileum Vit B-12 + Intrinsic factor are absorbed by *Pinocytosis*.
N.B) *Some drugs interfere with Vit B-12 absorption e.g. Para-amino-salicylic acid (PASA), Neomycin, Colchicine & Metformin.*
3- Cyanocobalamine is carried in blood by:
a- Mainly *Transcobalamine II* → β-Globulin.
b- Less *Transcobalamine I* → α-Globulin.
4- Concentrated in Liver & Kidney. They contain about 1 mg = 1000 ug.
5- Daily requirements of Vit B-12 is about 1 – 2 ug.
6- Rich sources of Vit B-12 → Meat, liver, fish & egg yolk.
7- Commercially Vit B-12 is obtained from extracts of Streptomyces griseus.
8- *Excretion*:
a- Bile → Entero-hepatic circulation.
b- Kidney → 0.25 ug / day.

* Functions of Vit B-12;

1- *Nucleo-protein synthesis* → Maturation of Epithelial cells & Hematopoiesis.
2- *Neuronal* function & myelination. 3- Liver → Lipotropic.

N.B.) Pernicious Anemia:

1- *Cause*: ↓ *Intrinsic Factor* e.g. Achlorhydria & Gastrectomy → ↓ Absorption of Vit B-12.
2- *Manifestations*:
a- Blood picture → Macrocytic hyperchromic anemia.
b- G.I.T. → Defective epithelization → Beefed tongue.
c- Neurological → Peripheral neuritis with spinal cord affection.

* Therapeutic Uses of Cyanocobalamine:

1- Treatment of **Pernicious anemia**:
   a- Dose: start by 1000 ug / day for 2 weeks then 100 - 1000 ug / month for life.
   b- Effect:
      - Correct bone marrow & blood picture → Appearance of Reticulocytes.
      - Correct of G.I.T. e.g. beefed tongue But Not achlorhydria.
      - Arrest of nervous manifestations.
2- Prophylaxis of **pernicious anemia** after gastrectomy.
3- As Lipotropic with hepatotoxic agents e.g. Halothane.

* Preparations:

1- Liver extract injection → May cause allergy.
2- Cyanocobalamine I.M.
3- Hydroxocobalamine I.M.:
   a- More bound to tissue proteins → More retained in body.
   b- Useful in pernicious anemia & in Cyanide poisoning.
4- Cyanocobalamine + Intrinsic factor → Orally.

2- Folic Acid

Conjugated Folic acid —(Cyanocobalamine)→ Free Folic acid —(Cyanocobalamine + Vit C + D.H.F.R.E.)→ Folinic Acid

1- Folic acid occurs as an inactive conjugated form mainly in yeast, liver, fresh green vegetables & fruits. 50-95% of folic acid content in food is destroyed by prolonged cooking or by canning.

2- Folic acid is reduced enzymatically in mucosa of Duodenum & upper Jejunum to Folinic acid (Tetra-hydro-folic acid = THFA) by Di-hydro-folate reductase enzyme (D.H.F.R.E.) by the aid of Vit B-12 & Vit C.

3- Folinic acid acts as co-enzyme in nucleo-protein synthesis & Erythropoiesis.

4- Daily requirements of Folic acid = 50 ug, that increases during pregnancy.

5- Uses & Dose: 10 – 20 mg / day orally
   a- **With Vit B-12** in treatment of Pernicious anemia.
      Folic acid alone → Corrects blood pictures But Worsens neurological manifestations.
   b- Increased daily requirements e.g. Pregnancy.
   c- Megaloplastic anemia due to mal-nutrition or mal-absorption.
   d- Long use of Anti-Epileptic drugs e.g. Phenytoin → Interferes with Folic acid absorption & ↑ Its metabolism (Phenytoin is an enzyme inducer).
   e- Long use of Di-hydro-folate reductase enzyme inhibitors
      → Better use Folinic acid rather than folic acid:
      - Anti-Bacterial → Trimethoprim.
      - Anti-Malarial → Pyrimethamine & Proguanil.
      - Anti-Metabolite → Methotrexate → Anti-cancer & immuno-suppressant.

Agranulocytosis & Aplastic Anemia

* Causative Agents:

1- Anti-Pyretic Analgesics e.g. Pyrazolone derivatives → Dipyrone.
2- Anti-Rheumatics e.g. Gold therapy.
3- Anti-Epileptics → Trimethadione.
4- Anti-Thyroid → Propyl thiouracil.
5- Anti-Microbials → Chloramphenicol.
6- Anti-Cancer → Cytotoxic drugs.

* Precautions:

1- Frequent complete blood count (C.B.C.).
2- Any infection e.g. Sore throat or Fever → Stop the drug & do C.B.C.

* Management:

1- Stop the offending agent.
2- Fresh blood transfusion.
3- Antibiotics e.g. penicillins.
4- Glucocorticoids e.g. Prednisolone.
5- Vit B-12 & Folic acid.
6- Anabolics.
7- Hemopoietic Growth Factors → Erythropoietin & Colony-Stimulating Factors.

.N.B.) Erythropoietin (Epoetin S.C. & I.V.):

1- Glycoprotein hormone produced by the kidney. Prepared by rDNA technology.
2- ↑ Proliferation & differentiation of R.B.Cs.
2- Used in anemia of Chronic Renal Failure.
3- Adverse Effect → Hypertension.

.N.B.) Colony Stimulating Factors (CSFs):

1- Cytokine glycoprotein. Prepared by rDNA technology.
2- ↑ Proliferation, differentiation & activity of neutrophils, monocytes & macrophages.
3- Preparations:
   a- Granulocyte/Macrophage-CSF (GM-CSF, Sargramostim) S.C. & I.V.
   b- Granulocyte-CSF (G-CSF, Filgrastim) S.C. & I.V.
4- Uses:
   a- Drug-induced Neutropenia e.g. cancer chemotherapy.
   b- After bone marrow transplantation.
   c- A.I.D.S.
5- Adverse Effects: Bone pain & allergy.

Met-Hemoglobinemia ($Hb\text{-}Fe^{3+}$)

1- Causative Agents: Nitrites & Nitrates, Phenactin, Primaquine & Sulfonamides.
2- Treatment: Ascorbic acid & Methylene blue (Excess Methylene blue → Met-Hb).

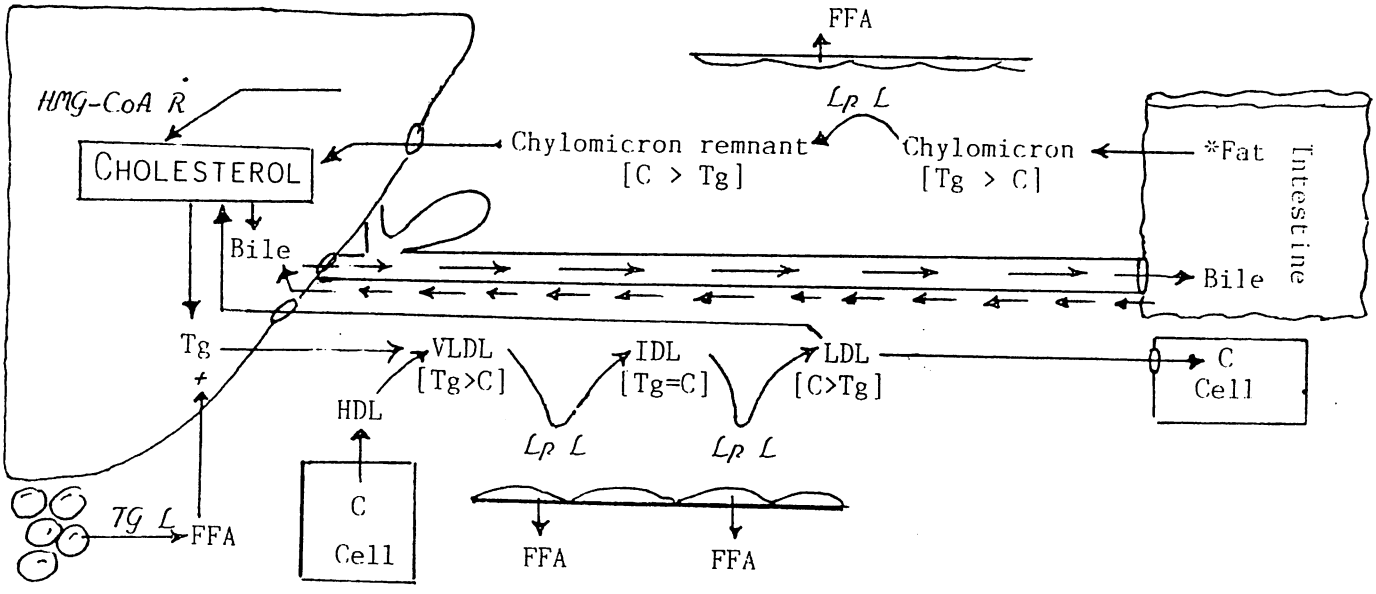
Hemolytic Anemia

1- Antigenic → α-Methyl-Dopa.
2- Direct effect → Lead.
3- Idiosyncrasy → Favism (Glucose-6-Phosphate-Dehydrogenase Enzyme Deficiency): Primaquine, Aspirin, Sulfonamides & Broad beans.

Management of Hyperlipoproteinemia

A) Diet Regulation:

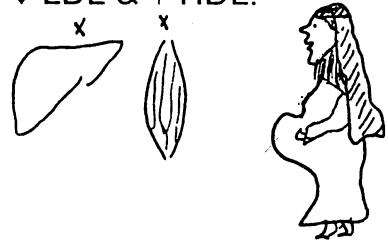
1- ↓ Caloric.
b- ↓ Cholesterol.
c- ↓ Saturated fatty acids: Animal fat.
d- ↓ Fat containing long chain fatty acids.
d- ↑ Unsaturated fatty acids: Vegetable oils.
e- ↑ Dietary fibers.
f- Stop smoking and alcohol drinking.
g- Avoid → β-Blockers (especially without ISA), Thiazide & loop diuretics.



B) Drug Therapy:

1- Hydroxy-Methyl-Glutaryl (HMG) Co-A Reductase Inhibitors :

1- **Examples :** **Lovastatin** *(Lowchol)*, **Pravastatin** *(Lipostat)*, **Simvastatin** *(Zocor)*, **Fluvastatin** *(Lescol)* & **Atrovastatin** *(Lipitor)*
2- **Mechanism** : Inhibit the synthesis of cholesterol → ↓ LDL & ↑ HDL.
3- **Side Effects** :
a- Hepatotoxic → ↑ Serum transaminases.
b- Myositis → ↑ Serum creatine kinase.
c- Contraindicated during pregnancy and lactation.



2- Bile Acid-Binding Resins :

1- **Examples:** **Cholestyramine** *(Questran)* & **Colestipol**.
2- **Mechanism:** They bind with bile acids to prevent their action and absorption.
a- ↓ Absorption of cholesterol.
b- ↓ Absorption of bile → ↑ Conversion of cholesterol to bile.
c- ↓ Cholesterol → ↓ LDL & ↑ HDL.
3- **Side Effects:**
a- Constipation.
b- Cholestero gall stones.
c- ↓ Absorption of most drugs : Digoxin, warfarin and fat soluble vitamins e.g. Vit K.

3- β-*Sitosterol:* Plant sterol, similar to cholesterol → ↓ Absorption of cholesterol.

4- *Neomycin:* Aminoglycoside antibiotic → ↓ absorption of bile acids & cholesterol.

5- *Fibric Acid Derivatives (Fibrates):*

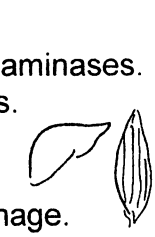
1- Examples: Clofibrate, Bezafibrate *(Bezalip)*, **Fenofibrate** *(Fenolip)*, **Etofibrate** *(Lipo-Merz)* **& Gemfibrozil** *(Lopid)*.

2- Mechanism:

a- ↑ Lipoprotein lipase enzyme.
b- ↓ Hepatic synthesis of truglycerides.
c- ↓ Triglycerides → ↓ VLDL.

3- Side Effects:

a- GIT upset. b- Gall stones. c- Gain weight.
d- Myositis → ↑ Creatine kinase. e- Hepatotoxic → ↑ Transaminases.
f- Skin rash, alopecia, impotence. g- Displace anticoagulants.
h- Contraindicated in :
- Liver & kidney diseases. - pregnancy & lactation.
- Not combined with HMG Co-A R ↓ → Severe Liver & Muscle damage.



6- *Nicotinic Acid (Niacin):*

1- Mechanism: ↓ Triglyceride lipase → ↓ FFA → ↓ Hepatic synthesis of triglycerides → ↓ VLDL (Tg) → ↓ IDL → ↓ LDL (Cholesterol).

2- Side Effects:

a- Itching & Flushing due ↑ PGs. Prevented by NSAID e.g. aspirin.
b- GIT disturbances. c- Hyperglycemia. d- Hyperuricemia.

NB) Acipimox: Similar to niacin with less side effects.

7- *Probucol:* Antioxidant. ↓ LDL.

8- *d-Thyroxin:* ↑ Cholesterol conversion to bile & ↑ its excretion in stool.

9- *Estrogens:* ↓ Cholesterol in males, but → Feminization.

10- *Fish oil = Omeg-3 Fatty acids:* ↓ Tg BUT ↑ Cholesterol.

NB) Combination Therapy of Anti-dyslipidemics:

1- HMG-CoA reductase inhibitors + Bile acid-binding resin → ↓↓ Cholesterol.
2- HMG-CoA reductase inhibitors + Nicotinic acid → ↓↓ BOTH cholesterol & Tg.
3- Gemfibrozil + Bile acid-binding resin → ↓↓ BOTH Tg & cholesterol.
4- Do *NOT* combine Fibrate & HMG Co-A R ↓ → Severe Liver & Muscle damage.

Blood Transfusion

* Source of Blood:

1- **Human volunteers** = Homologous blood.
2- **Self donation** = Autologous blood e.g. preoperative.

* Storage:

In sterile plastic bags
1- Add citrate (anticoagulant) and dextrose (for RBCs metabolism).
2- Temperature 2 - 6°C.
3- Storage for 21 days, in first 4 days it is considered as fresh blood.

* Indications:

1- Blood loss (Hemorrhage): Restore blood volume.
2- Bleeding tendency (hypoprothrombinemia, thrombocytopenia, hemophilia & anticoagulant therapy): Supply coagulation factors. Use fresh blood.
3- Severe anemia: Restore Hb content → ↑ O_2 carrying capacity. Use Packed RBCs.
4- Agranulocytosis: Provide leukocytes.
5- Supply cholinesterase in:
   a- Anti-cholinesterase toxicity = Cholinergic crisis.
   b- Succinylcholine toxicity.
6- Exchange transfusion in hemolytic diseases.

* Transfusion Reactions :

1- Hemolytic ***Reactions***: Due to blood group incompatibility :
   a- *Manifestations*: Fever, rigors, dyspnea, hypotension, back pain and acute renal failure.
   b- *Prophylaxis*: Careful blood grouping and cross matching.
   c- *Treatment*:
      i- Stop the infusion.
      ii- Alkalinization of urine to prevent precipitation of acid hematin.
      iii- IV fluids + Mannitol & Frusemide to treat oliguria and anuria.
2- Pyrogenic (Febrile) ***Reaction***: Fever and rigors due to presence of impurities (pyrogens), hemolysis, allergic reactions or infection.
3- ***A***llergic reactions in sensitive patients.
4- ***A***ir embolism.
5- ***T***ransmission of diseases e.g. Hepatitis B & C, and AIDS.
   Infected blood may cause Endotoxic Shock with rapid death.
6- ***T***ransfusion Siderosis: Multiple transfusions in non-bleeding patients.
   Treatment by *Desferrioxamine* by IV pump.
7- ***C***irculatory overload → Acute right ventricular heart failure.
8- ***C***itrate toxicity due to repeated massive transfusions → Hypocalcemia & metabolic acidosis.

* Human Plasma :

A) Indications of Plasma Transfusion:

1- Excessive plasma loss e.g. Severe burns.
2- Hypoproteinemia e.g. Nephrotic syndrome.
3- Emergency transfusion where compatible blood is not available.

B) Types of Human Plasma:

1- Liquid plasma:

a- Prepared by centrifugation of citrated blood.
b- Stored at room temperature for years.
c- Before use it is mixed with glucose 50% to make a final concentration of 5%.
d- It is free from fibrinogen & prothrombin (coagulation factors).

2- Dried Plasma:

a- Prepared by freezing-drying plasma.
b- Stable for 5 years.
c- Before used it is dissolved in sterile D.W. or saline or glucose 2.5%+ NaCl 0.45%.

3- Fresh Frozen Plasma (FFP):

a- Prepared by freezing liquid plasma at –15°C and stored at this temperature.
b- Gentle thawing before use.
c- FFP can supply all coagulation factors.

C) Advantages of Plasma Over Whole Blood Transfusion:

1- Plasma can be stored for at least 2 years without deterioration, whereas blood can be stored only for 3 weeks.
2- Cross matching is not required in case of plasma transfusion, provided that pooled plasma is used.

* Plasma Components:

1- Human serum Albumin: Useful in hypoproteinemia to restore osmotic pressure.

2- Human Gamma Globulin: To prevent or attenuate infection e.g. measles.
NOT used to increase circulatory volume.

3- Human fibrinogen, Thrombin & Fibrin as coagulants (See Blood).

* *Plasma Expanders or Plasma Substitutes* :

1- An ideal plasma substitute should be:

a- Same colloid osmotic pressure and viscosity as the plasma.
b- Retained intravascularly for an adequate time until regeneration of plasma.
c- Non-Toxic, Non-antigenic & Non-pyrogenic.
d- Easily sterilized.
e- Stable on storage & ready for use.

2- Proteins derived from human blood e.g. human albumin.

3- Proteins derived from animal sources e.g. Gelatin Solution 5-6% in saline :

a- It should be warmed before injection. It is solid or semisolid at room temperature.
b- Interfere with blood grouping.
c- Contraindicated in renal impairment.

4- Dextrans 6% solution in saline :

a- Polysaccharide synthesized from glucose by certain microorganisms.
b- Dextran 40 (MW 40 000) & Dextran 75 (MW 75 000)
c- Disadvantages :Interfere with blood grouping, Antigenic & Histamine releaser → Urticaria & joint pain.

5- Synthetic Products e.g. Polyvinyl Pyrrolidone (PVP):

a- MW 40 000.
b- Not metabolized, Non-Toxic & Non-Antigenic.

* *Crystalloids:*

They are used to restore lost fluids & electrolytes because they are poorly retained in vascular system.

1- Saline: Isotonic (0.9% NaCl) & Half tonic (0.45% NaCl).
2- Isotonic Dextrose (Glucose) 5%.
3- Ringer's solution: Na, K & Ca Chlorides.
4- Lactate Ringer's solution: Na, K & Ca Chlorides + Na lactate.

* *Correction of Disturbed Electrolytes & Acid/Base Balance:*

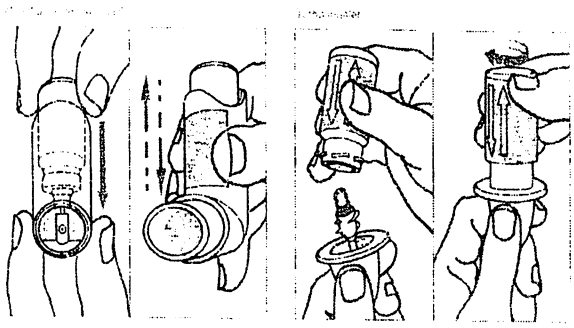
1- Sodium Loss:

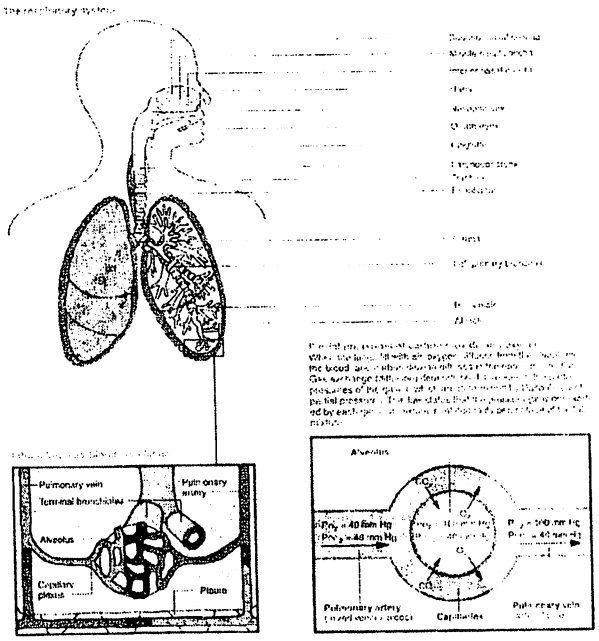
a- Proportionate loss of Na & water: Isotonic saline.
b- Loss of Na > Water : 3% NaCl solution.
c- Diarrhea associated with acidosis Saline (3/4 volume) + Sodium lactate 1.85% or 1/6 molar (1/4 volume).
d- Severe vomiting with alkalosis: Saline (Na will restore electrolyte, while Cl^- will correct acidosis).

2- Plain water loss e.g. diabetes insipidus: Glucose 5%, glucose → metabolized.

3- Potassium loss = Hypokalemia e.g. Diuretics, corticosteroids & insulin: Oral KCl or K citrate solution. I.V. administration is to be avoided to prevent toxic effect of K on heart.

Respiration





Gases & Vapors:

1- Therapeutic → Oxygen, Carbon Dioxide & Helium

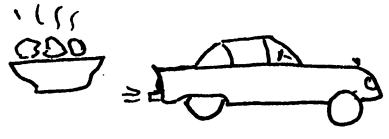
2- Noxious (Harmful) → Carbon Monoxide & Hydrocyanic acid.

Carbon Monoxide (CO)

Hb ♡→ CO

1- Hemoglobin (Hb) has High Affinity to CO = 210 times O_2 → Carboxy-hemoglobin (cherry red in color) → Inadequate for carrying O_2 & diminishes the O_2 releasing ability of the remaining Hb → Hypoxia.

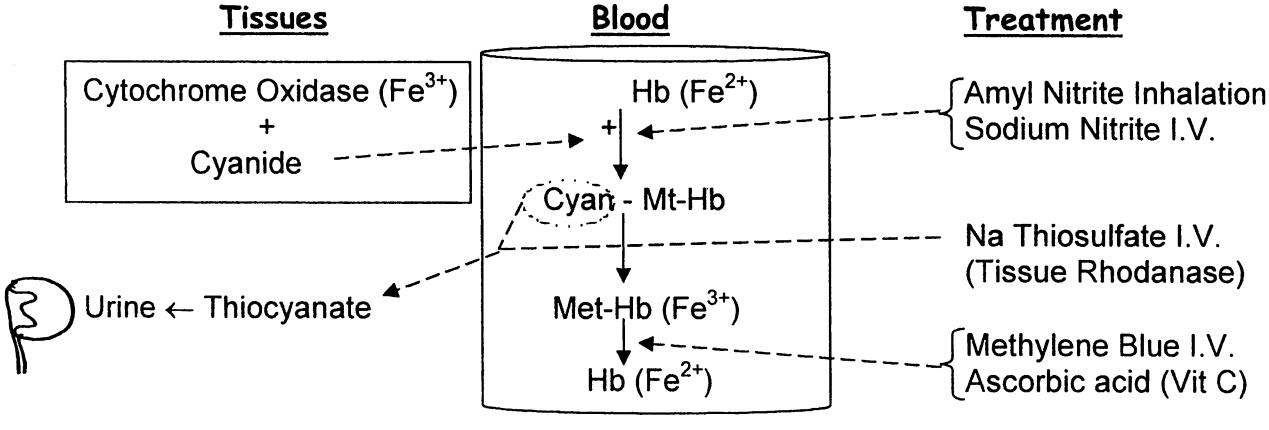
2- Treatment:
   a- Transfer the patient to Fresh Non-polluted air.
   b- Inhalation of Carbogen (CO_2 + O_2) or hyperbaric O_2.
   c- Supportive treatment.



Hydrocyanic Acid = Cyanide poisoning

Death within 5 minutes

Cyanide ♡→ Fe^{3+}



NB) Alternative Treatment by ***Chelating*** Agents e.g. Hydroxocobalamine I.V. or Di-cobalt Edetate I.V.

1- Cyanide has High Affinity to Trivalent Ferric Iron (Fe^{3+}).
2- Cyanide combine with Fe^{3+} of Cytochrome oxidase enzyme → A mitochondrial enzyme responsible for tissue respiration → Stop of tissue respiration → Histo-toxic hypoxia.
3- Death within 5 minutes.

* Treatment of Cyanide poisoning:

A) Long Method:

1- Amyl nitrite inhalation + Na Nitrite I.V. → Convert Hb (Fe^{2+}) to Met-Hb (Fe^{3+}).
2- Met-Hb + Cyanide → Non-Toxic Cyan – Met-Hb.
3- Sodium Thiosulfate I.V. → Chelates cyanide (needs tissue Rhodanase enzyme) → Thio-cyanate → Excreted in urine.
4- Methylene blue + Ascorbic acid (Vit C) I.V. → Reduce Met-Hb (Fe^{3+}) to Hb (Fe^{2+}).

B) Alternative (Short) Methods = Cyanide Chelating Agents:

1- **Hydroxocobalamine** I.V. + Cyanide → Cyanocobalamine (Vit B-12).
2- **Di-Cobalt Edetate** I.V. + Cyanide → Non-toxic easily excreted complex.

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Oxygen

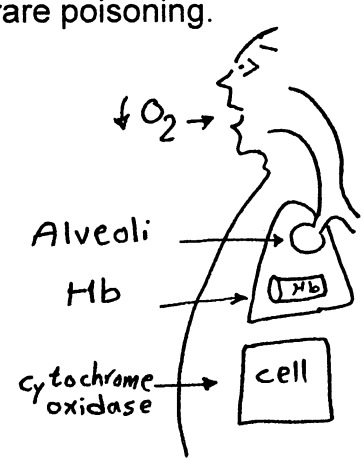
* Causes Of Hypoxia:

A) Inadequate Oxygenation of Normal Alveoli:

1- High altitudes.
2- Air-way obstruction e.g. Status asthmaticus.
3- Respiratory muscle weakness e.g. Myasthenia gravis & Curare poisoning.

B) Abnormal Pulmonary Function:

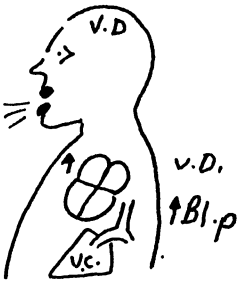
1- Pulmonary edema.
2- Emphysema.
3- Surgical removal.



C) Inadequate Oxygen Transport::

1- Little Hb e.g. Anemia.
2- Abnormal Hb e.g. Met-Hb, Carboxy-Hb & Sulf-Hb.
3- Slow circulation:
   a- Systemic e.g. Shock & Heart failure.
   b- Local e.g. Thrombosis.

D) Inadequate Tissue Respiration: Cyanide poisoning → Histo-toxic hypoxia.



* Manifestations of Hypoxia:

1- Cyanosis.

2- Reflex ↑ Respiratory Center (R.C.).

3- C.V.S.:

a- Reflex ↑ Sympathetic → ↑ Level of circulating catecholamines.
b- ↑ Heart rate, ↑ Bl.p., cerebral & coronary V.D. **BUT** Pulmonary V.C.

4- C.N.S.: According to arterial O_2 saturation:

a- 85% → ↓ Emotional stability, ↓ Mental efficiency, ↓ Visual acuity & ↓ Fine muscular coordination. زعلان ، مش فاهم ، مش شايف و حظي و حش
b- 75% → Faulty judgment, Marked muscle incoordination & Analgesia.
c- < 65% → Unconsciousness, Circulatory failure & Death.

* Therapeutic Uses of Normobaric Oxygen:

40-60% O_2 under positive pressure inhaled by:

- Nasal catheter
- Face mask
- Oxygen tent
- Endotracheal tube

1- Hypoxia *EXCEPT* Cyanide poisoning.
2- To dilute general anesthesia e.g. Halothane.
3- Abdominal distension e.g. Post-operative Paralytic ileus.
4- Migraine headache.

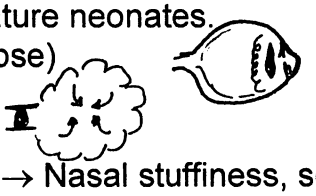
* Therapeutic Uses Of Hyperbaric Oxygen:

100% O_2 under High Atmospheric Pressure (2-3 Atmosphere) is special chambers.

1- **C**arbon monoxide poisoning.
2- **C**yanide poisoning.
3- **A**naerobic infection e.g. Gas gangrene.
4- **A**ir Embolism & Decompression sickness.

* Adverse Effects Of Oxygen:

1- Oxygen apnea.
2- Retro-lental fibrosis in Premature neonates.
3- Pulmonary Atelectasis (collapse) due bronchial obstruction.
4- Oxygen Poisoning:
   a- Respiratory tract irritation → Nasal stuffiness, sore throat & cough.
   b- C.N.S. → Twitches, vertigo, paresthesia, convulsions & loss of consciousness.



1-Neural (R.F.) → 3+
2-CO_2 → 2+ R.C
4-Hypoxia → 1+

Morphine & Barbiturates ↓ 1 &2

Carbon Dioxide (CO_2)

* Actions of CO_2:

1- C.N.S. → Depression

2- R.C. → Dual Analeptic on Normal R.C. & NOT desensitized one.

3- C.V.S.:

a- Directly: CO_2 ⟶ ↓ Heart + V.D.
b- Reflex: CO_2 → ↑ Sympathetic → ↑ Level of circulating catecholamines → ↑ Heart + V.C.
c- Net result → ↑ H.R., ↑ C.O.P. & ↑ Bl.p. + V.D. of Cerebral (Headache) & Coronary .

* Therapeutic Uses of CO_2:

1- Carbogen (2 – **5** – 10% CO_2 + O_2):

a- Carbon monoxide poisoning.
b- Hypoxia.
c- With inhalation anesthesia to accelerate induction & recovery from anesthesia.

2- CO_2 Snow (- 78°C):

a- Freezing local anesthetic.
b- Cauterant for warts & birthmarks.

3- Carbonated water (soda water) as carminative.

Helium (He)

1- Low density: 80 % He + 20% Oxygen → 1/3 density of air → Status asthmaticus.

2- Non-Inflammable: Added to explosive anesthetic mixtures e.g. Cyclopropane + O_2.

3- Low solubility in blood → Reduce decompression time after diving.

Cough Therapy

Cough is a protective mechanism to expel secretions & foreign bodies outside the respiratory tract.

* Types of Cough:

1- Non-Productive (dry or useless) → Treated by Anti-Tussives.
2- Productive (Useful) → Treated by Expectorants ± Mucolytic agents.

Anti-Tussives = Cough Suppressants

- Drugs **used** to suppress cough → Useful in Dry useless & Dangerous Cough.
- **Contra-indicated** in useful productive cough.
- **Classification**:
  1- Peripheral → ↓ Cough (Stretch) receptors along respiratory tract.
  2- Central → ↓ Cough center in the Medulla.

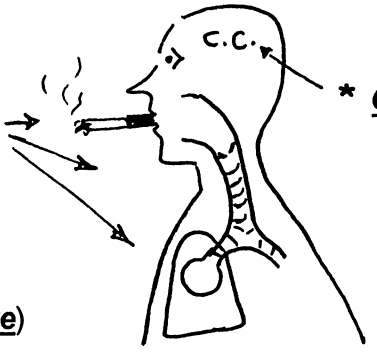
Anti-Tussives

Peripheral
↓ Cough receptors
1- Stop smoking
2- Liquorices
3-water steam
4- **Benzonatate***

Central
↓ Cough center in the Medulla

Opiate
- **Narcotic**
  - **Highly Addictive**: Morphine, Heroin, Methadone
  - **Less Addictive**: Codeine, Dihydrocodeinone, Pholcodine
- **Non-Narcotic**: Narcotine, Dextromethorphan, Levopropoxyphene

Non-Opiate
Benzonatate
Chlorphedianol
Oxeladine
Carbetapentane
Caramiphen



*** Peripheral Anti-Tussives**

1- Stop smoking
2- Pharyngeal demulcents
3- Water steam inhalation

4- Benzonatate (***DUAL Anti-Tussive***)

*** Central Anti-Tussives**

I- Anti-Tussives (Cough Suppressants)

A) Peripheral Anti-Tussives:

1- *Stop Smoking* → Treat smoker's cough.

2- *Pharyngeal Demulcent* e.g. **Liquorice** (Lozenge or Syrup) → Forms a protective coat & sooth irritated pharyngeal mucosa.

3- *Water Steam Inhalation* ± **Tincture Benzoin or Menthol.**

a- They ↑ bronchial glands to secret → Thin, soothing & protective mucus.
b- They are useful in treatment of Tracheo-bronchitis.

4- ***Benzonatate*** *(Tessalone):*

a- Chemically related to Procaine, a local anesthetic.
b- ***Dual*** Anti-tussive → Central (↓ Cough center) + Peripheral (↓ Cough "Stretch" receptors).

B) Central Anti-Tussives:

1- Opium Alkaloids:

a- Narcotic Opium Alkaloids:

- Highly Addictive → **Obsolete** e.g. Morphine, Heroin & Methadone.
- Less Addictive e.g. Codeine, Dihydrocodeinone & Pholcodine.

N.B.) Codeine Phosphate:

1- *Phenantherene* Opium Alkaloid. 1% of Opium.
2- Codeine (*Methyl Morphine*). 10% of Codeine → Morphine in the body.
3- *Weaker* than Morphine as Analgesic (1/5), Constipating, Addicting & ↓ R.C.
4- *Anti-tussive* = Morphine.
5- *Large dose* → Excitation & Epilepsy especially in Children.
6- *Anti-Tussive* (15-30 mg at Bed time) → Treat Dry useless & Dangerous cough.
7- *Analgesic* in Mild or Moderate visceral pain ± Aspirin ± Paracetamol.

b- Non-Narcotic Opium Alkaloids:

1- Narcotine (Noscapine): Benzylisoquinoline Opium alkaloid.
2- **Dextromethorphan** (Romilar): Synthetic substitute of Narcotine.
3- **Levopropoxyphene**: Non-analgesic Isomer of Dextropropoxyphene (Analgesic).

2- Non-Opiate Synthetic Derivatives:

1- Benzonatate. 2- Chlorphedianol. 3- Oxeladine.
4- Carbetapentane. 5- Caramiphen (Also Anti-Parkinsonian).
6- Anti-Histaminics (H_1-blockers) e.g. Diphenhydramine.

II- Expectorants

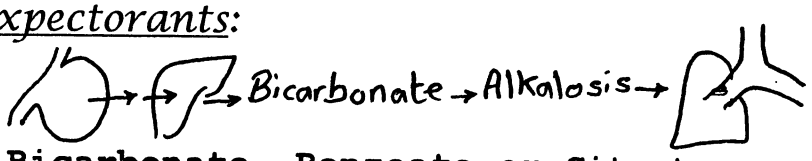
Drugs that help expulsion of viscid tenacious sputum

*** Classification:**

1- **Sedative Expectorant** → ↑ Secretion of *Thin, Soothing & Protective* bronchial mucus → Sedate acutely inflamed mucosa.
2- **Stimulant Expectorant** → Stimulate the healing of Chronically inflamed mucosa

A) Sedative Expectorants:

1- Alkaline Expectorants:

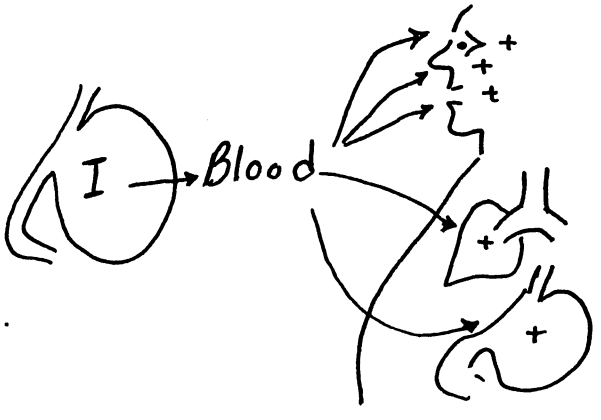


1- Na^+ or K^+ **Acetate, Bicarbonate, Benzoate** or **Citrate.**
2- They are transformed in body to Bicarbonate → Alkalosis.
Excess alkali → Excreted by Bronchial glands → Dissolve thick sputum & ↑ Bronchial mucus → Easy productive expectoration.
3- 1-2 g/1-2 hours → Treat Acute **B**ronchitis & **B**ronchial asthma (B & B).

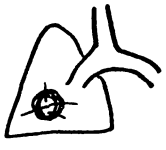
2- Nauseant Expectorants:

1- Sub-emetic dose of Tr. **Ipecacuanha** *(Emetine)*, Tr. **Senega** & **Ammonium** chloride or Carbonate:
2- Irritate gastric mucosa → Nausea → Reflex ↑ All secretions → ↑ Bronchial mucus.
3- Useful in **B**ronchitis & **B**ronchial asthma (B & B).

3- Saline Expectorant:



1- Na^+ or K^+ **Iodide.**
2- Absorbed orally from *Stomach* & intestine.
Secreted in *ALL* secretions → Irritation.
↑ Secretion of conjunctival, nasal, salivary & Bronchial glands → ↑ Bronchial mucus.
3- Iodide liquefies directly the tenacious sputum.
4- Therapeutic uses:
a- Chronic bronchitis & Bronchial asthma.
b- Hyperthyroidism *(See Hormones)*.
5- Adverse Effects:
a- Allergy → Skin rash.
b- ***Iodism*** → Headache, conjunctivitis, rhinitis, sialadenitis & gastritis.
6- Contraindications:
a- **A**llergy to iodine.
b- **A**cute bronchial asthma & bronchitis(Irritation).
c- **T**.B. Pulmonary.
d- **T**hyrotoxic patient under control by K^+ Perchlorate ($Iodide^-$ # $Perchlorate^-$).



B) Stimulant (Aromatic) Expectorants:

1- Examples: **Creosote, Guaiacol & Terpene hydrate.**

2- Actions:
- a- *Vulnerary* action → ↑ Healing of chronically inflamed bronchial mucosa.
- b- *Deodorant* action → Mask bad smell of pus.
- c- Mild antiseptic action.
- d- ↓ Secretion of sputum.

3- Therapeutic Uses:
- a- Chronic suppurative lung diseases e.g. Lung abscess & Bronchiectasis.
- b- ***NOT*** used in bronchitis or bronchial asthma.

Mucolytic Agents

- They liquefy viscid tenacious sputum.
- They are *NOT* expectorants, *But* they help the action of Expectorants.

1- Bromhexine *(Bisolvone):*

1- Bromhexine → Ambroxol (Active metabolite).
2- Depolymerizes the muco-poly-saccharides of ground substance of sputum.
3- Useful in Bronchitis & Bronchial asthma (B & B).
4- Dose: 8 – 16 mg / 6 – 8 hours.

2- Carboxymethylcysteine *(Mucodyne, Mucolase)*:

1- *Detergent* → Break the Bisulfide bridges (S-S) of sputum → ↓ Surface tension → Wetting and liquefaction of sputum → Mucolytic.
2- ↑ Volume of sputum *But* ↓ its Viscosity.
3- Prevent hyperplasia of mucous glands.
4- Useful in Bronchitis & Bronchial asthma (B & B).
5- Dose: 15 ml of 5% solution tds Orally.

3- Acetylcysteine:

1- *Detergent* similar Carboxy-methyl-cysteine.
2- *Therapeutic Uses*:
- a- Inhalation in bronchitis.
- b- I.V. or Orally to treat Paracetamol-induced Hepatotoxicity. It supplies the liver with S-H groups.

4- Enzymes:

1- Chemotrypsin & Trypsin → Orally.
2- Dornase alfa → Deoxyribonuclease → Inhalation.

Bronchial Asthma (الربو الشعبي)

Hypersensitivity & Hyperactivity of Bronchi

*Physiology:

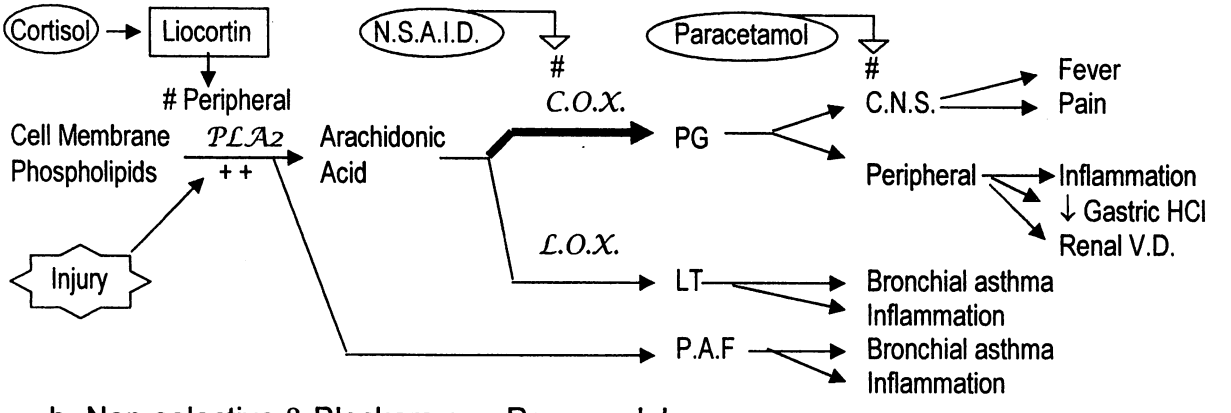
1- **Para**sympathetic nerve → A.Ch. → M_3 → Bronchospasm & ↑ Secretions.
2- **Symp**athetic nerve → Noradrenaline → α_1 → V.C. & ↓ Secretions.
Stimulation of postsynaptic α_1-adrenoceptors → Bronchospasm.
Rare type of bronchial asthma due to increase in bronchial α_1-receptors. α-blockers could be of value in management of some cases of bronchial asthma.
3- Adrenal **medulla** → Adrenaline → $\alpha_1 + \beta_2$ → Decongestion + Bronchodilatation.
4- **N**on-**A**drenergic **N**on-**C**holinergic (**NANC**) Mediators → Neuropeptides → Usually Bronchospasm → Play a role in pathogenesis of Bronchial asthma.
5- Most **Autacoids** (Except V.I.P & PGE_2) → Bronchospasm.
6- ↑ **cAMP** → Binding of Ca^{2+} → ↓ Free ionized Ca^{2+} → Bronchodilatation:
a- β_2-Agonists → ↑ G_S → ↑ Adenylate cyclase → ↑ CAMP.
b- Theophylline → ↓ Phosphodiesterase → ↑ cAMP.

*Predisposing Factors for Bronchial Asthma:

1- **Hypersensitivity** Reaction (Type I = Anaphylactic) → Extrinsic or Atopic asthma in response to Air-born allergens e.g. House dust mite:

Ag → Lymphocytes → IgE → Sensitize Mast Cells → Ag/Ab reaction → Release of mediators e.g. PAF & SRS-A
↳ Re-exposure to the same Ag ↑

2- **Rare** type of bronchial asthma due to increase in bronchial α_1-receptors.
3- Viral chest **infection** 4- **Occupational** 5- **Emotional** 6- **Exercise**
7- ***Pharmacological***:
a- Non-Steroidal-Anti-Inflammatory Drugs (NSAID) e.g. Aspirin → Block of COX pathway → Shift to LOX → LT → SRS-A → Bronchial asthma.



b- Non-selective β-Blockers e.g. Propranolol.
c- Parasympathomimetics.
d- Histamine, Histamine-like (Tolazoline) & Histamine-releaser (Morphine).

*Patho-physiology:

1- **Immediate** phase of *bronchospasm* caused by PGD_2, LT (SRS-A) & PAF.
2- **Late** phase of *Inflammation* caused by cytokines produced by T-lymphocytes e.g. IL, TNF, GM-CSF → Bronchospasm, V.D., Congestion, Edema, ↑ Mucus & cellular infiltration.

*Aim of Treatment:

1- Bronchodilatation. 2- V.C. & Decongestion. 3- Anti-inflammatory.
4- Liquefaction & expectoration of bronchial secretions.

*Management of Bronchial Asthma:

I- General Measures:

1- Identify the antigen:
   a- Avoid Antigen if possible b- Immuno-therapy → Hyposensitization.
2- Treat upper respiratory tract Infection e.g. sinusitis.
3- Yearly administration of Influenza vaccine every winter.
4- Stop Smoking.
5- Change the Job if possible.
6- Avoid Stress & Emotions.
7- Avoid severe muscle Exercise.
8- ***Avoid the following Drugs***:
   a- NSAID e.g. Aspirin:
      - If an Anti-pyretic analgesic is required → Use Paracetamol.
      - If an Anti-inflammatory is required → Use Corticosteroid.
   b- Non-selective β-Blockers e.g. Propranolol & even Timolol eye drops.
      - If a β-Blocker is required → Use small dose of Cardio-selective β_1-blockers e.g. Atenolol.
   c- Parasympathomimetics.
   d- Parasympatholytics e.g. Atropine → Dry bronchial secretions. Ipratropium is allowed.
   e- Histamine, Histamine-like & Histamine-Releasers.
   f- Anti-histaminics → Not very effective & Atropine-like.
   g- Barbiturates → ↓ R.C. Allow Benzodiazepines e.g. Diazepam.
   h- Narcotic Analgesics e.g. Morphine → ↓ R.C., ↓ Cough center, Histamine release & dry bronchial secretions.
   i- ACE-Inhibitors e.g. Captopril → ↑ Bk & PG. Allow AT_1-blockers e.g. Losartan.

*Drug Treatment of Bronchial Asthma:

A) Bronchodilators:

1- Sympathomimetics β_2-Agonists e.g. Salbutamol.
2- Parasympatholytics e.g. Ipratropium.
3- Methyl-xanthines e.g. Theophylline.
4- Leukotriene-Antagonists:
   a- 5-Lipo-oxygensae inhibitor e.g. Zileuton.
   b- Cysteinyl LT_1-receptor blockers e.g. Monelukast.

B) Anti-Inflammatory Drugs:

1- Mast Cell Stabilizers e.g. Di-Sodium Cromoglycate.
2- Anti-inflammatory Steroids e.g. Hydrocortisone.

C) Adjuvant Drugs:

1- If **S**putum → Mucolytic agents + Expectorants.
2- If **H**ydration is needed → I.V. fluids.
3- If **A**nxiety → Benzodiazepines e.g. Diazepam.
4- If **H**ypoxia → O_2 ± Helium.
5- If **I**nfection → Anti-microbials.

D) Drugs Under Trial:

1- PGE_2, *but* irritant.
2- K^+-Channel openers e.g. Cromokalim.
3- Calcium channel blockers.
4- Nitric oxide donors.
5- Anti-IgE monoclonal antibodies.
6- α_1-Blockers.

*Choice Of Drugs In Therapy Of Bronchial Asthma:

A) Therapy Of Acute Attack:

1- **Start** by Inhalation of a *Selective β_2*-Agonist e.g. Salbutamol (Metered Dose Inhaler)
2- **If No** adequate response → Aminophylline Slow I.V.
3- Expectorants & Mucolytics may be used to loosen viscid sputum.

B) Severe Acute Attack = Status Asthmaticus:

1- Hospitalization.
2- Oxygen 20% + Helium 80%
3- **Systemic Steroids**:
   a- Hydrocortisone Sodium Hemisuccinate or Methyl-Prednisolone I.V. Infusion / 4 hours till control of the attack. *Then*
   b- Prednisolone Orally for 2 days *Then* gradual withdrawal of Prednisolone.
4- **Bronchodilators**:
   a- β_2-Agonists e.g. Salbutamol.
   b- Methyl-xanthines e.g. Aminophylline.
5- *Hydration* by glucose 5%.
6- If *infection* → Antimicrobials.

C) Long Term Prophylaxis = Between The Attacks:

I- **General Measures** *(See before)*

II- **Drug Therapy**;
1- *Long acting β_2*-Agonists e.g. Salmeterol (Solution MDI) & Formoterol (Powder MDI)
2- *Theophylline* S.R. preparations.
3- *Ipratropium* (MDI)
4- *Leukotriene-Antagonists*.
5- *MASt Cell Stabilizers* e.g. Di-SodiumCromoglycate.
6- *Steroids*:
   a- Inhalation e.g. Beclomethasone (MDI).
   b- Oral e.g. Prednisolone.

I- Sympathomimetics (see A.N.S.)

*Mechanism Of Action:

1- ↑ β_2-receptors → ↑ G_S-protein → ↑ Adenylate cyclase enzyme → ↑ cAMP → ↓ Ca^{2+}:
   a- Bronchodilatation.
   b- ↓ Bronchial secretion & Improve muco-cilliary clearance.
   c- Mast cell stabilization → ↓ Release of Allergotoxins.
2- Some ↑ α_1-receptors → V.C. → Decongestion & ↓ Edema

*Members:

1- *Non-Selective β-Agonists*:

a- **Catecholamines**: Adrenaline ($\alpha + \beta_1 + \beta_2$) & Isoprenaline ($\beta_1 + \beta_2$).
b- **Non-Catecholamines**: Orciprenaline ($\beta_2 > \beta_1$) & Ephedrine ($\alpha + \beta_1 + \beta_2 +$ ↑ C.N.S).

2- *Selective β_2-Agonists*:

a- **Short Acting**: Salbutamol, Terbutaline, Hexoprenaline, Fenoterol & Rimiterol.
b- **Long Acting**: Salmeterol & Formoterol.

II- ANTI-CHOLINERGICS

1- Atropine → Not recommended in bronchial asthma due to:

a- Parasympathetic tone is Not an important cause of most of cases of bronchial asthma.
b- Dries bronchial secretions & inhibit muco-ciliary clearance.
c- Tertiary amine → Absorbed → Systemic side effects.

2- Iptratropium bromide (Atrovent) :

1- Synthetic **Quaternary** Ammonium Compound → NOT Orally & NOT pass BBB.
2- **Atropine** Derivative → Bronchodilatation BUT does *NOT* Dry bronchial secretions *Nor* affect muco-ciliary clearance.
3- Used ONLY by **Inhalation** in **Prophylaxis** of asthma & COPD (Slow Onset = 1-2 hours). 20 ug / Puff M.D.I. 1-2 Puffs / 2 - 4 times / day.
4- Patients with closed angle **glaucoma** should not use Ipratropium by Nebulization.

3- Oxytropium bromide:

1- Synthetic **Quaternary** ammonium compound derivative of **Hyoscine**.
2- Similar to Ipratropium.

4- Tiotropium bromide *(Spiriva):*

1- Synthetic **Quaternary** ammonium compound similar to Ipratropium *But*:
   a- More **potent** (10 times) & **Longer** duration
   b- 18 ug / puff M.D.I. od particularly useful in C.O.P.D.

III- METHYL XANTHINES

* *Mechanism of Action*:

1- Inhibition of **Phosphodiesterase Enzyme IV** → ↑ cAMP → ↓ Ca^{+2} :
   a- Broncho-DILATATION.
   b- Mast Cell Stabilization → ↓ Release of Mediators → ↓ Its Degranulation.

2- Block of **Adenosine Receptors**.

3- Release of *Catecholamines* & ↓ COMT.

4- Improve contractions of *diaphragmatic* contractions by mobilization of Ca^{+2}.

* *Members*:

A) Aminophylline (Theophylline Ethylene Diamine) :

1- **Uses & Doses:**

a- **Acute Attack** of Asthma: 250 - 500 mg ***S L O W*** IV injection.
   - To potentiate Sympathomimetics.
   - Substitute Sympathomimetics when they are Ineffective (Down-Regulation) or Contraindicated (Angina or Thyrotoxicosis).

b- **Status asthmaticus**: IV injection & Infusion as adjuvant to Hydrocortisone.

c- **Prophylaxis**:

   - *Day-time* Prophylaxis: ORAL Slow Release (SR), 200 mg/12 hs with meals.
   - *Nocturnal* Prophylaxis: Rectal suppository.

2- Side Effects of Theophylline:

1- **Narrow Safety Margine**:
a- Therapeutic plasma level = 10 - 20 ug / ml.
b- Toxic Plasma level = > 20 ug / ml.
2- **C.N.S.** : Headache, Nervousness, Insomnia & Convulsions (Seizures in Children).
3- **C.V.S.** : Tachycardia, Palpitation, Arrhythmia or Arrest & Hypotension (Rapid IV).
4- **G.I.T.** : Orally → Anorexia, Nausea & Vomiting. Rectally ↑ Proctitis in childtren.

3- Drug Interactions of Theophylline:

1- ↓ Metabolism by:
a- Cimetidine. b- Antimicrobials: Erythromycin & Quinolones.
c- Heart & Hepatic Diseases, and Hypothyroidism.

2- ↑ Metabolism by:
a- Rifampicine. b- Anti-Epileptics: Phenobarbitone, Phenytoin & Carabamazepine.
c- Hyperthyroidism d- Tobacco (Heavy smokers) & Alcohol.

B) Choline Theophyllinate: Similar to Aminophylline *BUT* Less Irritant.

C) Enprofylline: Similar to Theophylline *BUT*:
1- *More* Potent. 2- Does *NOT* Block Adenosine Receptors.
3- *Not* Diuretic. 4- *Not* Metabolized.
5- *Less Toxic*: NO CNS or CVS. May cause Headache & Nausea.

IV- Leukotriene Antagonists

They are useful mainly in NSAID-induced bronchial asthma. They are allowed in children > 6 years.

1- **5-Lipo-oxygenase inhibitor**: *Zileuton (Zylfo).*
2- **Cysteinyl LT_1-receptor blockers**: Montelukast *(Singular)*, Zafirlukast *(Accolate)* & Pranlukast *(Ultair)*.

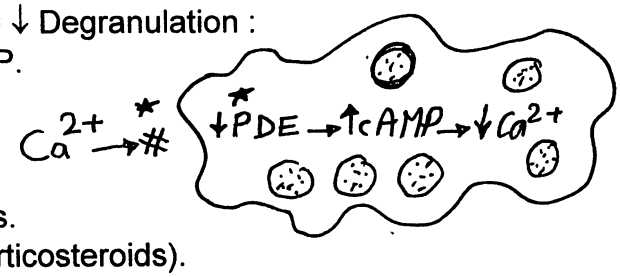
V- Anti-Inflammatory Anti-Asthmatics

* Mast Cell Stabilizers

A) Disodium Cromoglycate (Intal, Cromolyn Na) & Nedocromil Na⁺ (Tilade):

1- Mechanism of Action :
a- **Mast cell stabilizer** = ↓ Release of Mediators = ↓ Degranulation :
- Inhibits Phosphodiesterase enzyme → ↑ cAMP.
- Inhibits Ca^{+2} influx into mast cells.

b- Other Mechanisms → **Anti-iflammatory**
- ↓ Axon-mediated release of Neuropeptides.
- ↓ PAF interactions with platelets & Eosinophils.



2- Does **NOT** ↓ Antigen/Antibody Reaction (Unlike Corticosteroids).
3- Does **NOT** produce bronchodilatation (Unlike Sympathomimetics).

4- It is **NOT** effective in Acute Attacks of Asthma.
5- **U s e s**: ***PROPHYLAXIS*** specially of Extrinsic Asthma in Children.
   a- Long Term Prophylaxis. Re-Evaluate after one month.
   b- Immediate (Acute) Prophylaxis before exposure to Antigen or Exercise.

6- It is **NOT** effective Orally.

7- **D o s a g e**:
   a- **Inhalation** of Microfine POWDER by SPINHALER, 20 mg 4 times / day.
      Pretreatment by β_2-Agonist → Bronchodilatation → Helps Distribution.
   b- **Inhalation** of Solution by Nebulizer or Metered Dose Inhaler (MDI).
   c- **Nasal Spray** (Nasalcrom & Rynacrom 2%) for Allergic Rhinitis.
   d- **Ophthalmic Solution** (Optocrom 4%) for Allergic Conjunctivitis.
   e- **Oral** (Nalcrom) for ulcerative colitis.

8- **Side Effects** → Irritation → Bronchospasm, sense of suffocation, wheeze & cough.

B) K e t o t I f e n (Zaditen):

1- Similar to Sodium Cromoglycate **B U T**:
2- Effective **ORALLY**, 1 mg / 12 hours. Used in Prophylaxis of Asthma & Rhinitis.
3- Strong **Anti-Histaminic** (H_1-Blocker) & **Anti-Serotonin**.
4- **Side Effects**: Drowsiness.

* C O R T I C O S T E R O I D S

* Mechanism of Action:

1- Synthesis of *Lipocortin* → ↓ Phospholipase A_2 → ↓ Arachidonic Acid (PG & LT) & PAF
2- Decreases Antibody formation.
3- Inhibits Antigen/Antibody Reaction.
4- Mast Cell Stabilization = ↓ Release of Mediators = ↓ Degranulation.
5- Decrease cellular response to Inflammatory mediators.
6- Anti-inflammatory & ↓ Capillary Permeability →
   ↓ Inflammatory Edema of Bronchi → ↑ Airway caliber.
7- ↑ cAMP → ↓ Ca^{+2}.
8- Prevents Down-regulation of β_2-receptors.

* Members of Corticosteroids :

1- *Hydrocortisone Sodium Hemisuccinate* :

A- drug of choice in status asthmaticus.

b- **Dose**: IV injection & Infusion 200 mg / 4 - 6 hours till control of the attack.

c- Its effect appears after several hours (4-6 hours).

d- *Methyl-Prednisolone* is an alternative

2- *Steroids Aerosols for Inhalation* (MDI or Dry powder inhalation):

- ***Beclomethasone*** Dipropionate *(Becotid)*.
- ***Betamethasone*** Valerate *(Bextasol)*.
- ***Triamcinolone*** Acetonide *(Azmacort)*.
- ***Budesonide*** *(Pulmicort)*.
- ***Flunisolide*** *(AeroBid)*.
- ***Fluticasone*** *(Flixotide)*

a- Uses of Steroid Aerosols:

- Failure of other measures e.g. β_2-Agonits, Xanthines & Mast Cell Stabilizers.
- Recurrent disabling Asthma.
- Repeated nocturnal Asthma.
- Morning chest tightness.

b- Side Effects:

- Oropharyngeal Candidiasis (Thrush). Can be avoided by the use of Spacing device.
- Dysphonia → Change in voice.

c- Contraindications:

- Mild attacks of Asthma that would respond to other measures.
- Asthma with uncontrolled Chest Infection e.g. T.B.

3- *PrednIsolone*: ORALLY

a- Indications:

- Prophylaxis of Asthma after failure of Steroid aerosols.
- Maintenance after IV Hydrocortisone an Status Asthmaticus.

b- Side Effects & Contraindications: See Hormones.

VI- *Expectorants & Mucolytic Agents*

They liquefy & help expectoration of thick viscid & tenacious sputum.

1- **Alkaline expectorants**: Na^+ or K^+ Acetate, Bicarbonate, Benzoate or Citrate.
2- **Nauseant expectorants**: Ammonium carbonate, Tr. Ipecacuanha & Tr. Senega.
3- **Saline expectorants**: Sodium or Potassium Iodide.
4- **Mucolytic agents**: Bromhexine & Carboxymethyl-cysteine.

VII- *Oxygen Therapy*

1- Oxygen 40 – 60 % under pressure.
2- 20% Oxygen + 80% Helium → 1/3 Density of air.
3- Indicated whenever respiratory distress → Cyanosis, Hypoxia, Hypercarbia or Respiratory acidosis.

VIII- *Sedative & Tranquillizers*

1- Used to sedate the patient and alleviate effect of emotions on bronchial asthma.
2- Small doses of Bz e.g. Lorazepam or Chloral hydrate.
3- Avoid barbiturates & Narcotic analgesics.

IX- *Anti-Microbials*

1- Broad spectrum antimicrobials to treat any chest infection.
2- Penicillins & Cephalosporins are not recommended due to their liability known to produce allergy.

NB) Recent Approach to Bronchial Asthma:

A) Classification:

1- Mild Intermittent Asthma (Step 1) → Symptoms occur < twice/week & asymptomatic in between.
2- Mild Persistent Asthma (step 2) → Symptoms occur > twice/week.
3- Moderate Persistent Asthma (Step 3) → Daily symptoms + Exacerbation > twice/week.
4- Severe Persistent Asthma (Step 4) → Continuous symptoms with limited physical and frequent exacerbations.

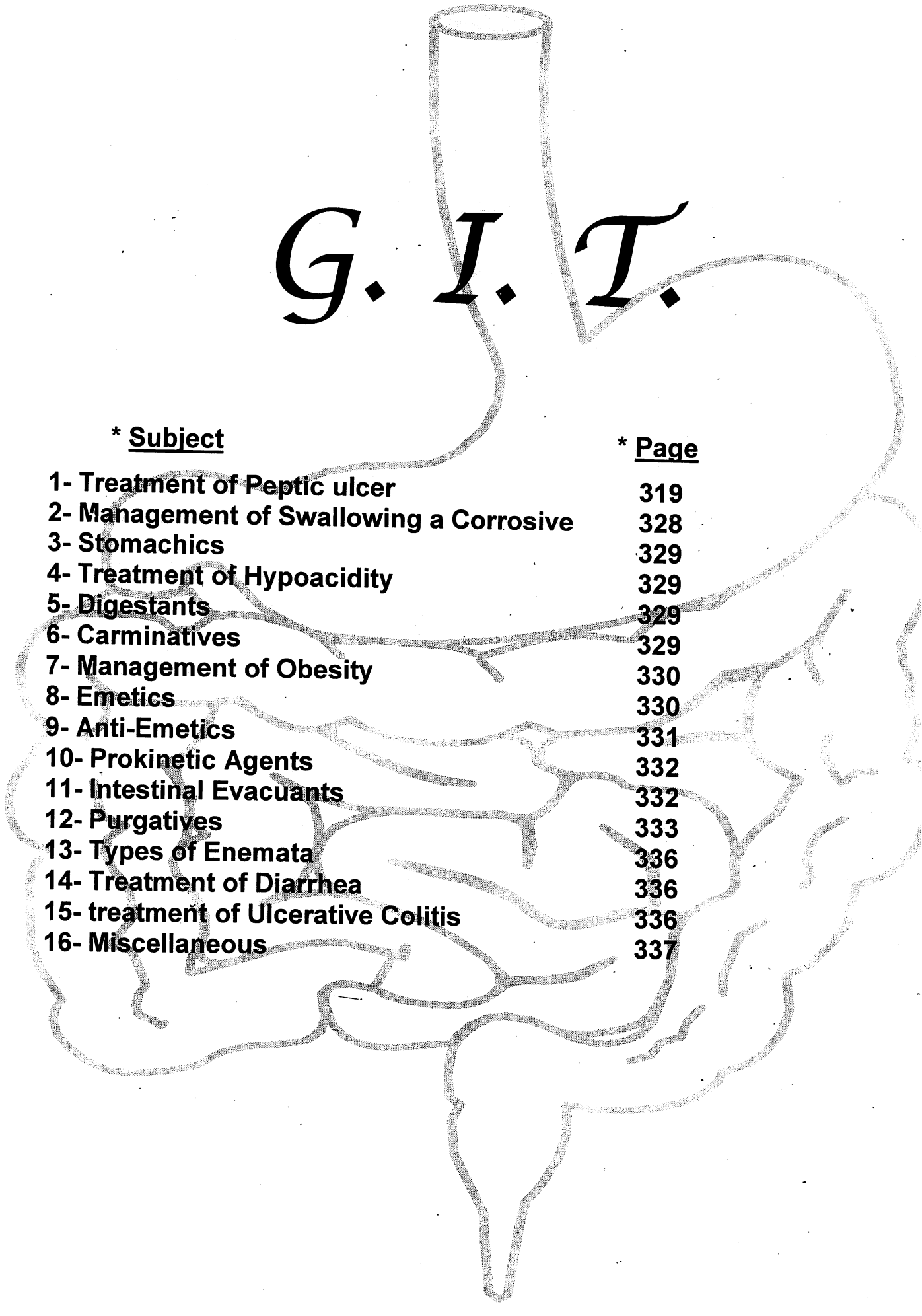
B) Management:

1- For quick relief → Inhaled β_2-Agonist e.g. Salbutamol.
2- In Mild Intermittent Asthma (Step 1) → NO need for daily prophylaxis.
3- In Mild Persistent Asthma (Step 2) → Daily Prophylaxis by:
   a- Low dose Inhaled Corticosteroid e.g. Beclomethasone. ***OR***
   b- Cromolyn Sodium (Intal) or Nedoromil. ***OR***
   c- Sustained release Theophylline. ***OR***
   d- Leukotriene antagonist e.g. Montilukast.
4- In Moderate Persistent Asthma (Step 3) → Daily Prophylaxis →
   a- Moderate dose of Corticosteroid +
   b- Long Acting Bronchodilator:
      - Long Acting β_2-Agonist e.g. Inhaled Salmeterol.
      - Slow release Theophylline.
5- In Severe Persistent Asthma (Step 4) → Daily Prophylaxis:
   a- High dose of Inhaled Corticosteroid +
   b- Long term use of Oral Corticosteroids +
   c- Long acting bronchodilator (β_2-Agonist or S.R. Theophylline).

If symptoms are NOT controlled:

i- Hospitalization.
ii- Oxygen 40 – 60%.
iii- Inhaled β_2-Agonist.
Iv-Ipratropium inhalation.
v- Hydrocortisone 200 mg I.V. / 4-6 hours for 24 hours
then Oral Prednisolone for 2 weeks.

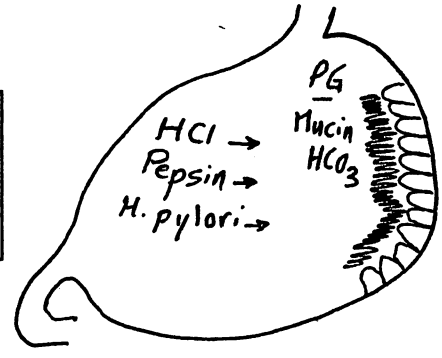
G. I. T.



Treatment of Gastric & Duodenal Peptic Ulcer

* Patho-physiology:

1- Aggressive Factors:	2- Defense Mechanisms:
a- HCl.	a- Prostaglandins.
b- Pepsin.	b- Mucus.
c- Helicobacter Pylori.	c- Bicarbonates.



* Clinical Features:

1- Symptoms & Signs:
   a- Epigastric pain & tenderness. b- Anorexia, Nausea & Vomiting. c- Hemorrhage.
2- Endoscopy.
3- Presence of H. pylori : Endoscopic biopsy, serological test & Urea breath test.

* Goals of Therapy:

1- Relief of pain. 2- Promotion of healing. 3- Prevention of recurrence.

* Drug Therapy:

A) Antacids (Neutralization of secreted HCl):

- Aluminum Hydroxide + Magnesium hydroxide or Trisilicate.

B) Antisecretory Drugs (Reduction of Acid Secretion):

1- **H_2-Receptor Blockers**: Cimetidine.
2- **Proton Pump Inhibitor (H^+/K^+ ATPase Inhibitors)**: Omeprazole.
3- **Antimuscarinic Drugs**: Pirenzepine.
4- **Gastrin Antagonists**: Proglumide.
5- **Prostaglandins**: Misoprostol.

C) Mucosal Protectives (Enhancement of Mucosal Resistance):

1- Sucralfate. 2- Colloidal bismuth.
3- Carbenoxolone. 4- Prostaglandins : Misoprostol.

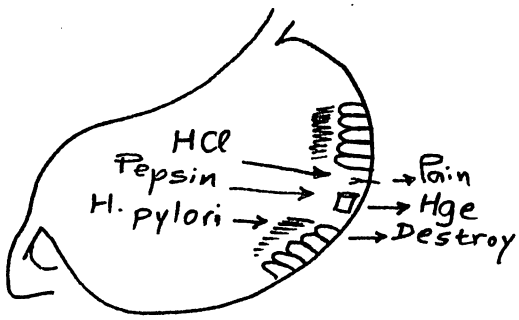
D) Eradication of H. pylori:

1- Metronidazole. 2- Bismuth compounds.
3- Amoxicillin. 4- Tetracycline.
5- Clarithromycin.

E) Other Drugs:

1- **Sedatives or Tranquillizers** e.g. Phenobarbital or Diazepam → # Psychic effect on acid secretion.
2- **Estrogen** on Males → But feminization.
3- **Tricyclic Antidepressants** → # Psychic effects + Anti-cholinergic + H_2-block.

Antacids



* They Produce:

1- Neutralization of HCl → Relief of Pain.
2- Elevation of pH → ↓ Activity of Pepsin.
3- Some → ↑ PGs & Eradication of H. pylori.

* Useful in treatment of:

1- Peptic Ulcer → Rapid relief → Supplement other drugs during initiation of treatment.
2- Gastro-Esophageal Reflux Disease (GERD) & Heart burn.
3- Gastritis

* Classification:

1- Chemical Anti-Acids.
2- Physical Anti-Acids.

I- Chemical Antacids

* **Systemic Antacids ($NaHCO_3$)** → Soluble & Absorbable → Systemic Alkalosis.
* **Local Antacids (Others)** → Insoluble & Not Absorbed → No Systemic Alkalosis

1- Sodium Bicarbonate ($NaHCO_3$):

* Advantage: Soluble → Quick onset.

* Disadvantages:

1- Short Duration.
2- CO_2 release → Distention, Discomfort, Rupture & Rebound Hyperacidity.
3- **Systemic** Alkalosis → Worsens Tetany.
4- Alkalinization of urine:
   a- Precipitate phosphate stones.
   b- ↓ Excretion of weak base drugs e.g. Ephedrine.
5- Hypernatremia → Contraindicated in Heart Failure & Hypertension.

* Therapeutic Uses:

1- Heart burn & NOT peptic ulcer.
2- Correct systemic acidosis.
3- To ↑ urinary excretion of weak acid drugs e.g. Salicylates & Barbiturates.
4- To ↑ urinary excretion of Uric acid → Treat Gout.
5- To potentiate Sulfonamides & ↓ crystaluria.
6- Urinary tract infection:
   a- Potentiate Streptomycin & Sulfonamides.
   b- Inhibit growth of bacteria.
   c- Relief of dysuria.
7- Alkaline expectorant.

2- Calcium Carbonate ($CaCO_3$):

* Advantages:

1- Quick onset.

2- Long Duration.

* Disadvantages:

1- CO_2 Release : Distention, Discomfort, Rupture & Rebound.
2- **Constipation**.
3- Hypercalcemia & Hypercalcuria.
4- Alkalosis.
5- Milk-Alkali syndrome → Severe constipation, alkalosis, hypercalcemia & hypercaluria.
6- ↑ Gastrin secretion → Rebound hyperacidity.

3- Magnesium Oxide & Hydroxide (Milk of Magnesia):

* Advantages:

1- NO CO_2 Release.
2- NO systemic Alkalosis or Alkaline urine.
3- Long duration.
4- Dose: $Mg(OH)_2$ 7 – 8 % aqueous suspension → 5 – 15 ml.

* Disadvantages:

1- Delayed onset.
2- **LAXATIVE** effect : Osmotic & Release of Cholecystokinin. (ملّين)

4- Magnesium Trisilicate:

Mg Trisilicate + HCl → $MgCl_2$ + H_2O + Silicon Dioxide GEL.

* Advantages:

1- Very EFFECTIVE Antacid. It acts Chemically and Physically :
   a- Chemical neutralization of HCl.
   b- Physically by formation of Silicon Dioxide GEL:
      - Adsorbs HCl & pepsin.
      - Demulcent effect on the ulcer floor.
2- NO CO_2 release.
3- NO systemic alkalosis.
4- Long duration.
5- Useful in patients with constipation.
6- Dose = 1 g.

* Disadvantages:

1- Delayed onset.
2- **LAXATIVE** effect: Osmotic & release of Cholecystokinin. (ملّين)

5- *Aluminum Hydroxide GEL:*

* Advantages:

1- Similar to Magnesium Trisilicate (1-4).
2- Useful in patients with diarrhea.
3- Dose = 8 ml.

* Disadvantages:

1- **Astringent** → Constipation (Add Mg Trisilicate = BEST COMBINATION).
2- ↓ Absorption of Phosphate → Hypophosphatemia.
   a- Useful in treatment of Hyperphosphatemia, phosphate renal stones & Hypocalcemia.
   b- Can be avoided by using Aluminum Phosphate GEL.
3- IF Renal Impairment → Toxicity: Encephalopathy, Osteodystrophy & Myopathy.

6- *Magaldrate :* $Mg(OH)_2 + Al(OH)_3$.

II- Physical Antacids:

They act by *ADSORBING* HCl & Pepsin and by *DEMULCENT* effect on the ulcer.

1- Gastric mucin.
2- $Al(OH)_3$ & $Al PO_4$ GEL.
3- Magnesium Trisilicate : It releases Silicon Dioxide GEL.
4- Anion Exchange Resin.

NB)

1- Time of administration: 1 – 3 hours after meals (Food neutralizes or buffers HCl for about 1 hour) & at bed time. Duration of action usually 2-3 hours.
2- Tablets (sucked or chewed) are more convenient for patients at work.
   Liquids act more rapidly & more suitable for frequent use.
3- Some Mg & Al antacids contain high content of Na as a hidden ingredients → May be harmful e.g. in cardiac patients.

NB) Drug Interactions of Antacids:

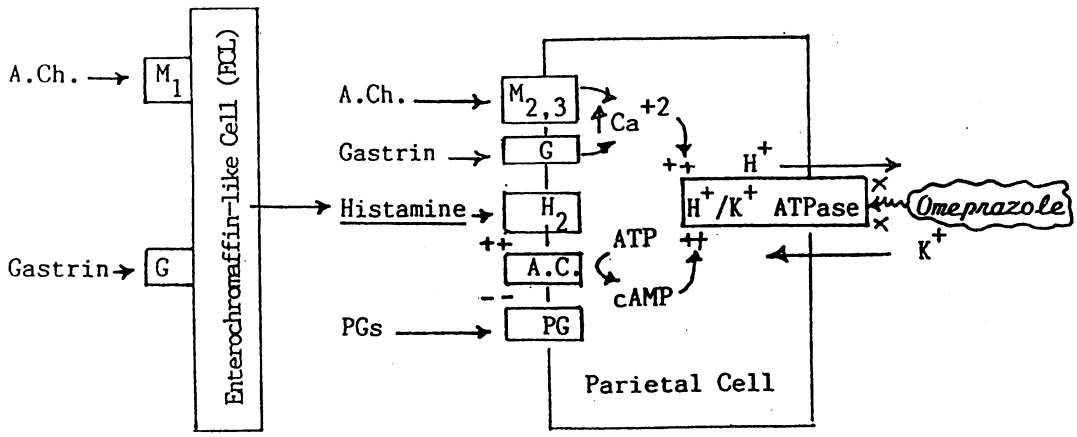
A) Affect oral bioavailability of other drugs:

1- Change pH of bowel content.
2- Adsorption or chelation.
3- Changing time of gastric emptying or transit time.
4- Examples:
   a- Ca^{+2}, Mg^{+2} & Al^{+3} ↓ absorption of Tetracyclines.
   b- Mg^{+2} & Al^{+3} ↓ Absorption of Warfarin, Ranitidine, Digoxin, Theophylline, Iron, Quinolones (Antibiotic) & Ketoconazole (Antifungal).

B) Antacids ↓ effect of Sucralfate as it needs acid medium to act.

Anti-Secretory Drugs

They inhibit the secretion of gastric HCl.



A) Anti-Muscarinic Drugs:

1- ***Pirenzepine*** (50 mg bid Orally for 4-6 Weeks) & ***Telenzepine*** →
Selective M_1-blockers → ↓ Acidity > ↓ Motility.
More effective when used with other drugs e.g. H_2-blockers.

2- ***Propantheline*** (15 mg qid), ***Oxyphencyclamine*** (10 mg bid) & ***Oxyphenonium*** (5 mg tds) → ↓ Motility > ↓ Acidity.

B) Gastrin Antagonists:

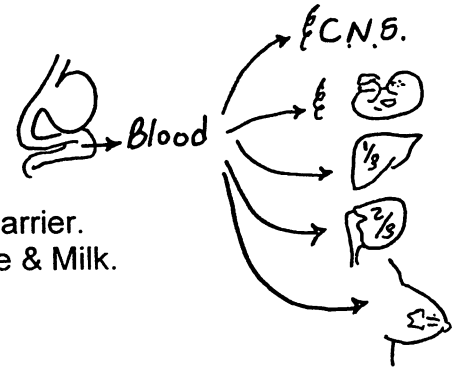
1- ***Proglumide***: Gastrin-receptors Blocker.
2- ***Somatostatin & Octreotide*** (Synthetic Somatostatin): ↓ Release of gastrin.

C) Prostaglandins:

1- *Example* : ***Misoprostol*** (Synthetic analogue of PGE_1).
2- *Mechanism* : Misoprostol + PG receptor → G_i → ↓ Adenylate Cyclase → ↓ cAMP.
3- *Useful* in treatment of NSAID-induced peptic ulcer.

D) H_2 - Blockers:

1- Cimetidine *(Tagamet)*:



**** Pharmacokinetics:***

1- WELL Absorbed Orally & Parentally.
2- Distributed ALL over the body. Passes BBB & Placental barrier.
3- 1/3 Metabolized in liver. 2/3 Excreted Unchanged in Urine & Milk.

**** Pharmacodynamics:***

1- Selective Competitive Blocker of Histamine H_2-receptors.
2- Reduces gastric acidity:
a- ↓ Both volume & Hydrogen ion concentration.
b- ↓ ALL phases of gastric acid secretion → Basal, Nocturnal & Stimulated (Diet, Stress & drugs e.g. Histamine, gastrin & cholinergic).
3- ↓ Formation of pepsin → ↓ Daily amount NOT its concentration.
4- ↓ Secretion of Intrinsic factor (BUT NO pernicious anemia).
5- Does *Not* affect gut motility → Unlike Parasympatholytics
6- ↓ The effect of histamine on Heart (H_2 Mainly) & BV (H_1 Mainly & H_2).

* ***Therapeutic Uses of Cimetidine:***

1- **Peptic Ulcer** (Gastric & Duodenal):
   a- Promotes the healing of the ulcers & prevent their recurrence.
   b- Dose:
      - Either 800 mg before bed time or 400 mg bid Orally for 6-8 Weeks for duodenal Ulcer & More for Gastric Ulcer.
      - Maintenance 400 mg before bed time Orally for 6 Months.
      - Decrease the dose in Renal & hepatic patients.
2- **Ulcers** → Stress, Iatrogenic(eg NSAID) & Zollinger-Ellison syndrome (Use large doses).
3- I.M. or I.V. in **Upper G.I.T. bleeding** after burn, trauma or acute renal failure
4- **Gastro-Esophageal Reflux Disorders** (GERD) & Hiatal hernia.
5- **Pre-anesthetic** in emergency operation & labor to prevent aspiration of gastric HCl.
6- To treat manifestations of systemic **Mastocytosis**.

* ***Side Effects & Drug Interactions of Cimetidine:***

1- Sudden stop → Recurrence of the ulcer & Bleeding.
2- GIT Upsets → Constipation or diarrhea.
3- Hypersensitivity reactions e.g. Skin rash & Itching.
4- Affect liver & kidney (↑ Serum creatinine).
4- ↓ Hepatic blood flow → ↓ Metabolism of Lidocaine & Propranolol.
5- Hepatic Microsomal Enzyme Inhibitor (↓ Cytochrome P450):
   ↓ Metabolism of Warfarin, Theophylline, Diazepam & Phenytoin.
7- In Males (Anti-Androgen) → Gynecomastia & ↓ Spermatic count.
8- In Females → ↑ Prolactin → Galactorrhea & Infertility.
9- In Elderly : Mental Confusion.
10- Blood Dyscrasias : Agranulocytosis, Aplastic Anemia & Thrombocytopenia.
11- Muscle pain.

2- Ranitidine (Zantac):

1- Pharmacokinetics similar to Cimetidine ***BUT LONGER & NO BBB***.
2- Pharmacodynamics Similar to Cimetidine ***BUT STRONGER*** (5-10 Times).
3- Therapeutic Uses Similar to Cimetidine ***BUT BETTER***
   Dose : Either 300 mg before bed time or 150 mg bid Orally. Also IM.
   Maintenance dose 150 mg od po for 6 months.
4- Side Effects similar to Cimetidine ***BUT SAFER*** :
   a- Similar to Cimetidine (1-5 ONLY).
   b- ***NO*** Hepatic Microsomal Enzyme Inhibition.
   c- ***NO*** Anti-Androgenic.
   d- ***NO*** ↑ Prolactin.
   e- ***NO*** BBB → **NO** CNS in Elderly.

3- Famotidine (Pepcid):

1- Similar to Ranitidine ***BUT STRONGER*** (3-20 times).
2- Dose Either 40 mg before bed time or 20 mg bid Orally. Also IM.

4- Nizatidine (Axid):

1- Similar to Ranitidine & same dose either 150 mg bid or 300 mg at bed time.
2- ***NOT Metabolized*** → 100% Oral bioavailability.

E) Proton Pump Inhibitors (H^+/K^+ ATPase Inhibitors):

*** Examples:**

1- Omeprazole *(Losec)*: 20-40 mg od Orally & I.V.
2- Lansoprazole *(Lanzor)*: 15-30 mg od Orally
3- Pantoprazole *(Controloc)*: 20-40 mg od po
4- Rabeprazole *(Pariet)*: 20 mg od po

} For 4 Weeks (Duodenal Ulcer) and 8 Weeks (Gastric Ulcer)

*** Pharmacokinetics:**

1- Well absorbed orally. Affected by gastric acidity. Given as buffered or enteric coated preparation.
2- Concentrated in acid canaliculi of gastric parietal cells.
3- Hepatic metabolism. $T_{1/2}$ = 1 hr, BUT it affects gastric acidity for 2-3 days.
4- Metabolites are excreted in urine.

*** Pharmacodynamics:**

1- **Prodrugs**: Activated in the acid environment of the secretory canaliculi of the parietal cells of the stomach.
2- **Irreversible** inhibitor of H^+/K^+ ATPase enzyme.
3- ↓ Basal & Stimulated gastric acidity up to 100%. BUT NO effect on gastric motility.
4- ↑ Gastrin secretion.

*** Therapeutic Uses:**

1- Peptic ulcer & Zollinger-Ellison syndrome (Drug of Choice).
2- Gastro-Esophageal Reflux Disorder (GERD).

*** Side Effects:**

1- CNS : Headache, Dizziness & Drowsiness.
2- GIT : Nausea, Diarrhea & Abdominal colic.
3- Skin rash.
4- Omeprazole ↓ metabolism of Warfarin, Theophylline, Diazepam & Phenytoin.
5- In rats → Gastric Carcinoid tumors (? Due to Hypergastrinemia).

Mucosal Protectives

Enhancement of Mucosal Resistance

A) Prostaglandins (PGE_2 & PGI_2) :

1- **Example**: Misoprostol (Cytotec). Synthetic analogue of PGE_1.
Dose : 200 ug qid Orally.
2- **Mechanism**: Misoprostol + PG-R → G_i → ↓ Adenylate Cyclase → ↓ cAMP.
3- ↑ Mucus secretion → ↓ Back diffusion of HCl.
4- ↑ HCO_3 secretion.
5- ↑ Blood supply to mucosa.
6- ↓ H Cl secretion (Anti-Secretory).
7- Promotes healing of ulcer.
8- Prevent gastric ulcer induced by NSAID.
9- **Side Effects**:
a- Oxytocic → Abortion. Contraindicated in pregnancy.
b- Nausea & abdominal pain.

B) Carbenoxolone sodium (Biogastrone) :

1- Glycoside of Glycyrrhiza (Liquorice) roots.
2- Absorbed Orally. Enterohepatic circulation.
3- Promotes the healing of peptic Ulcers (Gastric & Duodenal) :
   a- ↑ Mucus secretion → ↓ Back diffusion of HCl.
   b- ↑ Local PGs by ↓ their inactivation.
4- Steroid = Similar to Aldosterone
   a- Mineralocorticoid activity → Na^+ & H_2O Retention (Edema) + K^+ Depletion (Hypokalemia).
      - Add Diuretic (Thiazide & NOT Spironolactone).
      - AVOID In Heart Failure & Hypertension.
      - Aggravates Digitalis toxicity.
   b- Its Ulcer healing effect is # by Spironolactone.

C) Sucralfate (Gastrofate , Carafate) :

1- Composed of *Sulfated Sucrose + Al $(OH)_3$*. It has NO acid neutralizing activity.
2- Activated *in presence of acid* → Forms a *complex gel with mucus* → Adheres to mucous membrane & Ulcer floor → Physical barrier → ↓ Back diffusion of HCl & prevents degradation of mucus by pepsin.
3- *Adsorbs* Pepsin & Bile → ↓ Peptic digestion.
4- ↑ Local *Prostaglandins*.
5- Promote healing of Gastric & Duodenal ulcers & prevent their recurrence.
6- *Side Effects*:
   a- Dry mouth, Indigestion & Constipation.
   b- ↓ Absorption of food.
   c- ↓ Absorption of Drugs : Cimetidine, Phenytoin, Digoxin, Tetracyclines, Fluoroquinolone Antibiotics & Ketoconazole.
   d- Side effects due to Aluminum (See before).
7- *Dose* 1 g / 6 hrs Orally ONE hour BEFORE meals.
   Requires acid pH for activation, so **NOT** administered with H_2-blockers or Antacids.

D) Colloidal Bismuth Compounds :

1- *Example*: Colloidal Bismuth Subcitrate (Tripotassium Dicitro-Bismuthate, Bismuth Chelate, De-Nol).
2- **B**inds to proteins of Ulcer floor → Protective layer.
3- ↑ PG synthesis, ↑ Mucus production & ↓ pepsin activity.
4- ***Bactericidal*** against Helicobacter pylori.
5- Weak Antacid activity.
6- Promotes the healing of Gastric & Duodenal peptic ulcers.
   As effective as H_2-blockers.
7- *Dose*: 240 mg bid Orally ½ hour before breakfast & bed time.
8- May cause ***Black*** color of oral cavity & stool.

Management of Peptic Ulcer

* General Measures:

A) Rest:

1- Mental rest : Minor tranquilizers may be used.
2- Physical rest in bed in acute hemorrhagic ulcer.

B) Diet:

1- Small frequent light meals.
2- Milk in reasonable amounts is suitable Milk contains:
   a- Proteins →
      i- Colloids → Demulcent effect on mucosa & adsorption of HCl and pepsin.
      ii- Amphoteric → Chemical neutralization of HCl.
   b- Fats → Enterogastrone hormone → ↓ Acidity and motility.
   c- However Excess milk → Excess Ca & Proteins → ↑ Gastrin → Rebound hyperacidity
3- Avoid:
   a- Heavy meals, spicy foods, vinegar, fried meat & meat extract.
   b- Beverages : Xanthines (Coffee & tea), Carbonated & Alcoholic.
   c- Smoking & Chewing gum.

C) Drugs *to be* ***AVOIDED*** :

1- Alcohol : Up to 10% Conc. → ↑ Gastric secretions & conc. > 40% → Irritation.
2- Xanthines : Caffeine → ↑ Gastric secretions. Theophylline → Irritation.
3- Tobacco → Irritation and ganglion stimulation (Nicotine SD).
4- Reserpine.
5- Tolazoline & Phentolamine → Histamine like.
6- Parasympathomimetics.
7- Anti-Inflammatory drugs :
   a- NSAID e.g. Aspirin → Irritation, ↓ PGs & ↑ Bleeding. *Paracetamol* is allowed.
   b- SAID e.g. Glucocorticoids & ACTH.
8- Histamine, Histamine like & Histamine releasers.
9- Stomachics & Digestatnts.
10- KCl oral preparation.

* Surgical Treatment:

May be required in *Complicated Cases* e.g. severe Hemorrhage, Perforation or Gastric outflow obstruction.

* Medical Treatment:

A) Active Ulcer Associated with H. pylori :

1- First Line :

a- Eradication of H. pylori : Triple therapy for 2 weeks

Metronidazole 250 mg tds Orally
+ Amoxicillin 500 mg tds Orally
+ Colloidal Bismuth subcitrate 240 mg bid orally.

b- Anti-Secretory Drug : One of H_2-blocker for 6-8 weeks

- Cimetidine 800 mg at bed time or 400 mg bid.
- Ranitidine 300 mg at bed time or 150 mg bid.
- Nizatidine 300 mg at bed time or 150 mg bid.
- Famotidine 40 mg at bed time or 20 mg bid.

2- Alternative Line :

a- Eradication of H. pylori : Double therapy for 2 weeks

Metronidazole 250 mg tds Orally
+ Amoxicillin 500 mg tds Orally or Clarithromycin

b- Anti-Secretory :

One of Proton pump inhibitor for 4 weeks (Duodenal Ulcer) & 8 weeks (Gastric ulcer)

- Omeprazole 20 mg bid Orally.
- Lansoprazole 30 mg / day Orally.
- Pantoprazole 20 mg od po
- Rabeprazole 20 mg od po

B) Active Ulcer NOT attributed to H. pylori :

Use ONE of the anti-secretory drugs EITHER H_2-Blocker or Proton pump inhibitor alone.

C) Prevention Relapse = Maintenance therapy for 6 months

1- H_2-Blockers : 1/2 the dose at bed time for 6 months

- Cimetidine 400 mg.
- Ranitidine 150 mg.
- Nizatidine 150 mg.
- Famotidine 20 mg.

OR

2- Sucralfate 1g 4 times daily on empty stomach, one hour before meals.

D) Treatment of Acute Hemorrhage complicating an Ulcer :

1- Bed rest.
2- Fresh blood transfusion → Anti-shock + coagulation factors.
3- Gastric lavage with ice-cold saline + suction of blood from the stomach.
4- Oxygen.
5- After control of bleeding and shock, give MILK 50-100 ml by gastric drip + Antacid e.g. Magnesium hydroxide (Avoid Aluminum & calcium salts → fecal impaction).
6- Continue for 48 hours, then start medical treatment as in active stage.

NB) Management of Swallowing a Corrosive e.g. Potash (البوتاس):

1- Neutralization by weak acid e.g. diluted vinegar and lemon juice.
2- Demulcents egg raw egg + milk.
3- Antibiotics to prevent infection.
4- Glucocorticoids to reduce inflammation & prevent fibrosis.
5- H_1-Antihistaminics.
6- Naso-gastric tube for feeding.
7- Dilatation of esophagus with gum elastic bougies.

Stomachics = فـــواتح الشـــهية

- These are drugs that improve appetite.
- They ↑ taste buds in tongue → ↑ Hypothalamus → ↑ Parasympathetic → ↑ G.I.T. motility & secretions.
- **They include**:

1- Ethyl alcohol up to 10%.
2- Spices (بهارات) e.g. Pepper.
3- Flavors e.g. Volatile oils.
4- Bitters (لواذع) :

They are taken sip by sip (شفطة شفطة) 1/4 hour before meals.

a- Simple bitters e.g. Quasia.
b- Aromatic bitters e.g. Orange peel, cinnamon (قرفة) & ginger (زنجبيـــل).
c- Astringent bitters e.g. Cosparia (كوسبرة) → It contains tannic acid.
d- Alkaloidal bitters e.g. Quinine (كينا) & Strychnine.

Treatment Of Hypoacidity

A) If Hypochlorhydria → Use drugs ↑ gastric parietal cells:

1- Drugs ↑ Cholinergic Mechanisms:

a- Parasympathomimetics: Bethanicol & Neostigmine.
b- Reflex ↑ Parasympathetic: Stomachic & Insulin (Hypoglycemia).

2- Meat Extract → ↑ Gastrin secretion.

3- Direct ↑ Gastric Parietal Cells:

a- Ethyl alcohol up to 10%.
b- Methyl-xanthine beverages e.g. Coffee & tea.
c- Histamine → ↑ H_2 + H_1 receptors.
d- Betazole → Selective H_2-Agonist.
c- Pentagastrin → Direct ↑ of parietal cells.

Used in Diagnosis of Achlorhydria = Pernicious anemia.

B) If Achlorhydria → Use Diluted HCl or Glutamic acid HCl orally.

Digestants

1- Stomachics.
2- Diluted HCl or Glutamic acid HCl orally.
3- Pepsin & Papain.
4- Pancreatin → Trypsin + Amylopsin + Lipase.

Carminatives

Expulsion of gases via the mouth = Eructation

1- Small doses of chloroform or ether.
2- Volatile oils e.g. peppermint, camphor, anise, caraway & cinnamon.
3- Carbonated water → CO_2 → ↑ Intra-gastric pressure → Overcome cardiac sphincter.

Management Of Obesity

A) Treat any underlying pathology IF Possible.

B) Balanced low caloric diet rich in fibers e.g. Bran.

C) Muscular exercise.

D) Other measures e.g. Acupuncture & Psychotherapy.

E) Drugs:

1- **Methylcellulose** → Bulk forming → Sense of satisfaction.
2- **Glucagon** → Hyperglycemic → ↑ Satiety center.
3- **Anorectic agents**:
   a- **Phenmetrazine** & **Diethylpropion** *(Tenuate)* → Amphetamine like → Liable for drug dependence.
   b- **Sibutramine** *(Meridia)* → ↓ Uptake of Noradrenaline & 5-HT → Hypothalamus → ↑ Satiety & ↓ Hunger. Contraindicated in Epilepsy & Cardiovascular diseases.
   c- **Metformin** *(Cidophage)* → Biguanide Oral Anti-Diabetic drug → Anorectic → Useful in Obese Non-Insulin Dependent Diabetics.
5- **Orlistat** *(Xenical)* → Potent & Irreversible inhibitor of gastric & pancreatic lipases → ↓ Digestion & Absorption of fat.
   Adverse Effects → Produces fatty/oily diarrhea & ↓ Absorption of fat-soluble vitamins.
6- **Fat burners**: **Octopamine** → ↑ β_3-Receptors → Lipolysis & Thermogenesis.

Vomiting

* Emetics:

- Drugs used to induce vomiting.
- Useful to evacuate stomach in cases of Oral poisoning.
- Used ONLY in conscious patients to avoid aspiration pneumonia.

A) Central Emetics: *Apomorphine* S.C. → ↑ D_2-receptors in C.T.Z.

B) Peripheral Emetics:

1- Rapidly Acting:

a- Warm saturated solution of table salt (NaCl). BUT if NO vomiting → Hypernatremia.
b- Copper sulfate ($CuSO_4$) in phosphorus poisoning. BUT if NO vomiting → Cu poisoning.

2- Slowly Acting:

a- Examples: **Tr. Ipecacuanha, Tr. Senega & Ammonium carbonate.**
b- Uses:
   - Emetic dose → Evacuate stomach in cases of oral poisoning.
   - Sub-emetic dose → ↑ Secretions → Diaphoretic, Sialagogue & Nauseant Expectorant.

NB) Vomiting & Anti-Emetics:

Most of vomiting → ↑ C.T.Z. (D_2 & 5-HT_3) → ↑ Vomiting Center (M & H_1) → Vomiting.

Motion Sickness →

Anti-Emetics

A) Centrally Acting Anti-emetics :

1- Hyoscine (Scopolamine): ½ mg ½ hr before the journey po or transdermal patch.

a- Blocks M-receptors in vomiting center.
b- Effective in ALL vomiting including Motion sickness.
Short acting → Useful in air sickness.

2- Anti-Histaminics :

a- Block H_1-receptor in vomiting center.
b- Effective in all vomiting including Motion sickness.
Long acting → Useful in sea sickness.

c- *Examples* : **Dimenhydrinate, Diphenhydramine, Promethazine, Meclizine & Cyclizine.**

3- Phenothiazines :

a- Block D_2-receptor in CTZ.
b- Effective in all vomiting EXCEPT motion sickness.
c- *Examples* : **Chlorpromazine**. Better avoid during pregnancy → Teratogenic.

4- Butyrophenones :

a- Block D_2-receptor in CTZ.
b- Effective in all vomiting EXCEPT motion sickness.
c- *Examples* : **Droperidol** & **Haloperidol**.

5- Metoclopramide *(Primperan)* :

a- **DUAL** anti-emetic :
- Centrally Blocks D_2-receptor in CTZ.
- Peripherally → ↑ Cholinergic mechanisms → ↑ Gastric motility.

b- Effective in all vomiting EXCEPT motion sickness.

6- Domperidone *(Motilium)* :

a- DUAL anti-emetic :
- Centrally Blocks D_2-receptor in CTZ.
- Peripherally → α-Blocking activity → ↑ Gastric motility.

b- Effective in all vomiting EXCEPT motion sickness.

7- Pyridoxine (Vit B-6) : Effective in vomiting of pregnancy.

8- Glucocorticoids :

- ACTH, Cortisol & **Dexamethasone** → Used in cancer chemotherapy-induced vomiting.

9- Serotonin 5-HT_3-Receptors Antagonists :

a- *Exemples* : **Ondansetron** *(Zofran)* & **Granisetron** *(Kytril)*.
b- Used orally & IV mainly in cancer chemotherapy-induced vomiting.

10- Cannabinoids e.g. **Nabilone**. Used in cancer chemotherapy-induced vomiting.

B) Peripheral Anti-Emetics :

1- Metoclopramide → Cholinergic effect → ↑ Gastric motility → Prokinetic agent.
2- Domperidone → α-blocking effect → ↑ Gastric motility → Prokinetic agent.
3- Demulcents & Local anesthetics : To prevent gastric irritation.

Prokinetic Agents

1- Metoclopramide *(Primperan, Plasil)*

*** *Pharmacodynamics* :**

1- Anti-Emetic : It has ***DUAL*** mechanism of action

a- Central : Blocks D_2-receptors & in LD it blocks 5-HT_3 receptors in CTZ.

b- Peripheral → ↑ Gastric motility → ↑ Gastric emptying → Prokinetic agent :

- Block D-receptors in stomach.
- Stimulate 5-HT_4 receptors in enteric ganglia → Release of A.Ch. → Muscarinic effect.
  This action is blocked by atropine.

2- Prokinetic agent → ↑ Gastric motility & emptying. This action is blocked by atropine.

*** *Therapeutic Uses*** : 10 mg 3-4 times/day Orally, Rectally, IM & IV.

1- All vomiting EXCEPT motion sickness.
2- Gastric hypomotility e.g. Diabetic gastroparesis.
3- Gastric ulcer.
4- Emergency evacuation of stomach before surgery or X-ray.
5- Gastro-Esophageal-Reflux-Disease (GERD, Reflux Esophagitis).
6- Hiccup.

*** *Side Effects* :**

1- Dizziness & nervousness.
2- Extrapyramidal manifestations e.g. Parkinsonism & ataxia.
3- Hyperprolactinemia → Galactorrhea in females.
4- ↑ Absorption of concomitantly administrated drugs EXCEPT Digoxin.

2- Domperidone *(Motilium)*

1- **Similar** to Metoclopramide → Dual Anti-Emetic & Prokinetic agent :
   a- Central : Block D_2-receptors.
   b- Peripheral : Block α-adrenoceptors in stomach → ↑ Motility → Prokinetic agent.
   This action is NOT antagonized by atropine.
2- **Limited** passage across BBB → Rare extrapyramidal manifestations BUT STILL can produce hyperprolactinemia.

3- Cisapride *(Prepulsid)*

1- ↑ 5-HT_4 receptors in enteric ganglia → Release of A.Ch. → ↑ Gastric & Colonic motility → Prokinetic agent. Uses similar to Metoclopramide (2-5).
2- NOT block D-receptors → NOT Antiemetic

Intestinal Evacuants

1- Purgatives.
2- Cleansing Enema.
3- Glycerin Suppository :
   a- Produces mild irritation of rectum and colon.
   b- Useful in adults & specially the CHILDREN.
4- Smooth Muscle Stimulants e.g. Parasympathomimetics such as Neostigmine.

Purgatives

- Drugs taken Orally to evacuate the bowel.
- They are either → Mild (Laxative) or Potent (Cathartic).

* Classification of Purgatives:

A) Physical:

1- **Bulk forming** e.g. Saline purgatives.
2- **Lubricant** e.g. Liquid paraffin.
3- **Surfactant** (Surface active agents) e.g. Dioctyl Sodium Sulphosuccinate.

B) Chemical (Irritant) Purgatives:

1- **Mild irritant** e.g. Castor oil (زيت الخروع).
2- **Moderate irritant** e.g. Phenolphthalein.
3- **Severe (Drastic) irritant** e.g. Croton oil (زيت حَبّ الملوك), Colocynth (الحنظل) & Jalap → Severe irritation & diarrhea → Dehydration, ulceration & perforation of G.I.T.

A) Physical Purgatives: (عيش - ملح - سكر - زيت - صابون)

1- Bulk Forming:

- They ↑ bulk of gastric & intestinal contents → Stretch of wall → Reflex peristalsis.
- They act on BOTH small & large intestine.
- Onset of action: 1 – 3 hours → Taken in the Morning.

1- **Food** containing unabsorbed residues e.g. Vegetables & Bran (رَدّة). (عيش)
Bran *is suitable & safe for chronic constipation in elderly.*

2- **Methyl-cellulose** → Hydrophilic granules.

3- **Plantago seeds & Agar** → Imbibe water.

4- *Saline Purgatives e.g. Magnesium Sulfate* ($MgSO_4$, Epsom's salt) (ملح)
a- Non-absorbable ***osmotic*** salt → retains water in bowel.
b- Release of Chole-Cysto-Kinin → Evacuate gall bladder → Bile → ↑ Peristalsis.
c- Dose: 15 g before breakfast in an isotonic solution (ملئ ملعقة كبيرة على كوب ماء كبير).
NB) Other Osmotic salts: Na_2SO_4 (Glauber's salt), MgO & $Mg(OH)_2$ = Magnesia milk

5- *Lactulose (Duphalac syrup):* (سكر)
a- Artificial sugar = Fructose + Galactose.
b- ***Osmotic***, Not digested & Not absorbed → Retain water in bowel.
c- Splited by Colon bacteria → Lactic acid + Others → lower pH of colon:
- Formation of soft stool.
- Inhibition of proteolytic bacteria → ↓ Formation of ammonia.

d- **Uses**:
- Constipation.
- **With neomycin (Aminoglycoside antibiotic → Kill proteolytic bacteria) in Hepatic encephalopathy.**

2) Lubricant Purgatives:

* Liquid Paraffin = Paraffin Oil: (زيت)

1- Synthetic mineral oil → Not absorbed orally.
2- Softens & lubricates hard fecal masses & mucosa of **large** intestine.
3- Onset of action: 8-10 hours.
4- Dose 15 – 30 ml at **night**.
5- Useful in **Chronic Constipation**.
6- **Disadvantages**:
   a- Bad consistency, so either add fruit juice or use an emulsion.
   b- ↓ Absorption of fat-soluble vitamins (A, D, E & K) →
      - ↓ Vitamin D → ↓ Ca^{2+} absorption → ↓ Growth & teething in children.
      - ↓ Vitamin K → Hypoprothrombinemia → Potentiate Oral Anticoagulants.
   c- ↓ Absorption of other drugs e.g. Oral Contraceptives.
   d- Uncontrolled leakage from anal sphincter →
      - Pruritis ani.
      - Anal polyp.
      - Delays healing of ano-rectal operations e.g. piles & fissures.
   e- If absorbed orally → Foreign body reaction in liver.
   f- If it reaches the lung → Lipid pneumonia.

3- Surfactants Surface Active Agents;

* Dioctyl Sodium Sulfosuccinate *(Normax)*: (صابون)

1- Anionic surface active agent → Surfactant = Detergent.
2- Lowers surface tension of hard fecal masses → Wetting & softening.
3- Dose: 200 mg at night.

B) Chemical (Irritant) Purgatives:

* Disadvantages & Contraindications of Irritant Purgatives:

1- Colic, diarrhea & dehydration → Add small doses of Atropine or Hyoscine.
2- ↓ Absorption of nutrients & drugs.
3- Pelvic congestion:
   a- Menstruation → Dysmenorrhea.
   b- Pregnancy → Abortion.
4- May be excreted in milk → Affect suckling baby.

1- mild Irritant Purgatives:

* Castor Oil (زيت خروع):

1- Fixed plant oil.
2- In **small** intestine —*Lipase & Bile*→ Glycerin + Ricinoleic acid.
3- Ricinoleic acid → Irritates **small** intestine → ↑ Peristalsis.
4- Dose 15 – 60 ml in the **morning**.

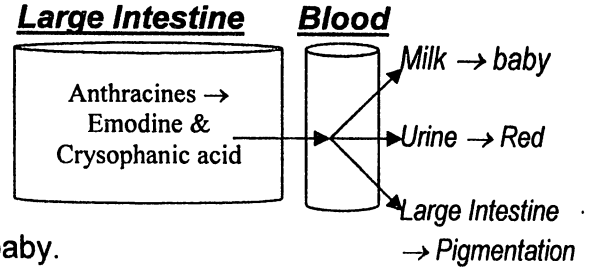
* **Figs (التين) & Prunes (قراصيا)** → Mild irritant + Bulk forming.

B) Moderate Irritant Purgatives:

* Anthracine (Anthraquinone) Derivatives:

1- **Examples**: **Rhubarb** (الراوند) , **Aloe** (صبر أو صبار), **Cascara** (كسكرة) & **Senna** (سنامكي).

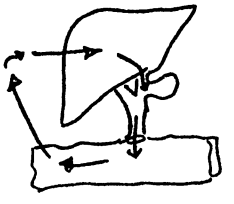
2- In **large** intestine they release *Emodine & Crysophanic acid* → Absorbed → Excreted in **Large** intestine → Irritation.



3- **Onset**: 6-12 hours → Taken at **night**.

4- **Disadvantages**:
   a- Colicky pain.
   b- Excreted in Milk → Diarrhea in suckling baby.
   c- Excreted in urine → Red discoloration of alkaline urine.
   d- Reversible melanotic pigmentation of colon mucosa → Melanosis coli.
   e- Purgative effect of Rhubarb is followed by constipation due to its high content of Tannic acid → Astringent.

* Phenolphthalein:



1- It is dissolved by Bile & Alkalinity in small intestine → Irritation.
2- Irritates small & mainly **Large** intestine.
3- It has Entero-Hepatic circulation → Long duration (3-4 days).
4- **Dose**: 0.1 - 0.2 g at **night**.
5- **Disadvantages**:
   a- Cumulation
   b- Liver damage
   c- Skin rash
   d- Red discoloration of alkaline urine

* Bisacodyl *(Dolcolax, Bisadyl)*:

1- Related to Phenolphthalein **BUT** NO entero-hepatic circulation → Shorter duration.
2- Effective orally (Purgative) & rectally (Suppository)

NB) Sodium Picosulfate *(Picolax)* is related to Bisacodyl.

* Therapeutic Uses of Purgatives:

1- Constipation:
   a- Acute: Saline ($Mg\ SO_4$) or irritant purgative.
   b- Chronic: Liquid paraffin or Dioctyl Na Sulfosuccinate + Diet regimen (Bran).
2- Oral food & drug poisoning → Saline ($MgSO_4$) purgative + Charcoal.
3- Before operation & X-ray abdomen.
4- Before & after some anti-helminthes e.g. Tinea solium → Saline purgative.
5- To avoid straining in some patients e.g. hernia & eye operations.

* Types of Enemata :

A) Evacuant (Cleansing, Purgative) Enema :

1- Large volume (1 L). 2- High head pressure. 3- Mild irritant e.g. Chamomile.

B) Retention Enemata :

1- Small volume (1/4 L). 2- Low head pressure. 3- Non-irritant.

4- *Examples* :

a- Nutrient : Glucose & pentose. b- Dehydrating : Saturated $MgSO_4$.

c- Basal anesthesia : Thiopentone. d- Anti-inflammatory : Cortisol.

e- Anti-parasitics. f- X-ray contrast media : Barium SO_4.

* Treatment of Diarrhea :

- Specific (Causative) Treatment : Treat the cause e.g. Cholera.
- Non-Specific (Symptomatic) Treatment :

I- Correction of Dehydration, Acid/Base & Electrolyte Imbalance :

A) In Mild & Moderate cases use **Oral Rehydration** Therapy (ORT) :

1- ORT does ***NOT*** cure diarrhea, BUT ***ONLY*** corrects dehydration, acid/base & electrolyte imbalance.

2- Powder containing Glucose (4 g) + Na Cl (0.7 g) + K Cl (0.3 g) + Na citrate (0.51 g) to be dissolved in 200 ml water.
The presence of glucose facilitates the absorption of Na^+, with subsequent Cl^- & H_2O.

3- Initially the patient takes one teaspoonful / min. till he is satisfied.
Then continue for 1-2 days after control of diarrhea.

4- Solution should not be stored for more than 24 hours.

B) In Severe cases use **Parenteral Rehydration** Therapy.

II- GIT Protectives :

1- **Adsorbents** : Kaolin, Bismuth, Chalk & Charcoal.

2- **Absorbents** : Pectin, which is present in rice, carrots, apple.

3- **Astringents** : Tr. Catecho → Release tannic acid in intestine.

III- Anti-Motility Agents :

1- **Parasympatholytics** : Atropine & Propantheline.

2- **Opiates** : Diphenoxyalte & Loperamide.

* Treatment of Ulcerative Colitis :

1- **Correct** anemia, dehydration, electrolyte & acid/base imbalance.

2- **Corticosteroids** : Cortisol & Prednisolone Orally, IV or Retention enema.

3- **Sulfasalazine** (Salazopyrine) : Orally.

a-NOT absorbed from small intestine.

b-Split in colon by bacteria into :

-Sulfapyridine → Absorbed → Most of side effects.

-Azo-link.

-5-Aminosalicylic acid → Blocks LTB_4-Receptors → Local anti-inflammatory effect.

4- **Mesalazine** : 5-Aminosalicylic acid. Taken orally. Safer than sulfasalazine.

5- **Olsalazine** : Two 5-Aminosalicylic acid linked by azo-link. Taken orally

* *Treatment of Colic = Anti-Spasmodic:*

1- **Parasympatholytics** e.g. Atropine, Propantheline & Hyoscine butyl bromide *(Buscopan)*
2- **Direct Spasmolytics**: Volatile oils (peppermint), Kheline, Papaverine, Nitrites & Nitrates (Nitroglycerine) & Aminophylline.
3- **Mebeverine** *(Colospasmine)* → *Direct spasmolytic* → Useful in colon spasm.
4- **Hot water bag** → Counter-irritant.

* *Treatment of Biliary Colic:*

1- **Atropine & its substitutes** e.g. Hyoscine butyl bromide (Buscopan).
2- **Nitroglycerine**.
3- **If severe pain** → Morphine + Atropine (Never morphine alone) or Meperidine alone.

* *Sialagogues* → Drugs ↑ salivary secretions e.g. Pilocarpine → Treat xerostomia.

* *Anti-Sialagogues* → Drugs ↓ salivation e.g. Atropine → Useful as Pre-anesthetic & in treatment of Parkinsonism.

* *Cholagogue* = Evacuate Gall bladder →
1- **$MgSO_4$** (2-4 g before breakfast):
a- Release Cholecystokinin → Contract wall of gall bladder.
b- Relax sphincter of Oddi.
2- **Fats & oils** → Release Cholecystokinin.
3- **Parasympathomimetics**.

* *Choleretics* = ↑ Synthesis of bile by heptocytes
1- Natural bile acids → Cholic acid & desoxycholic acid.
2- Synthetic derivatives → Na Glycocholate & Na Taurocholate.

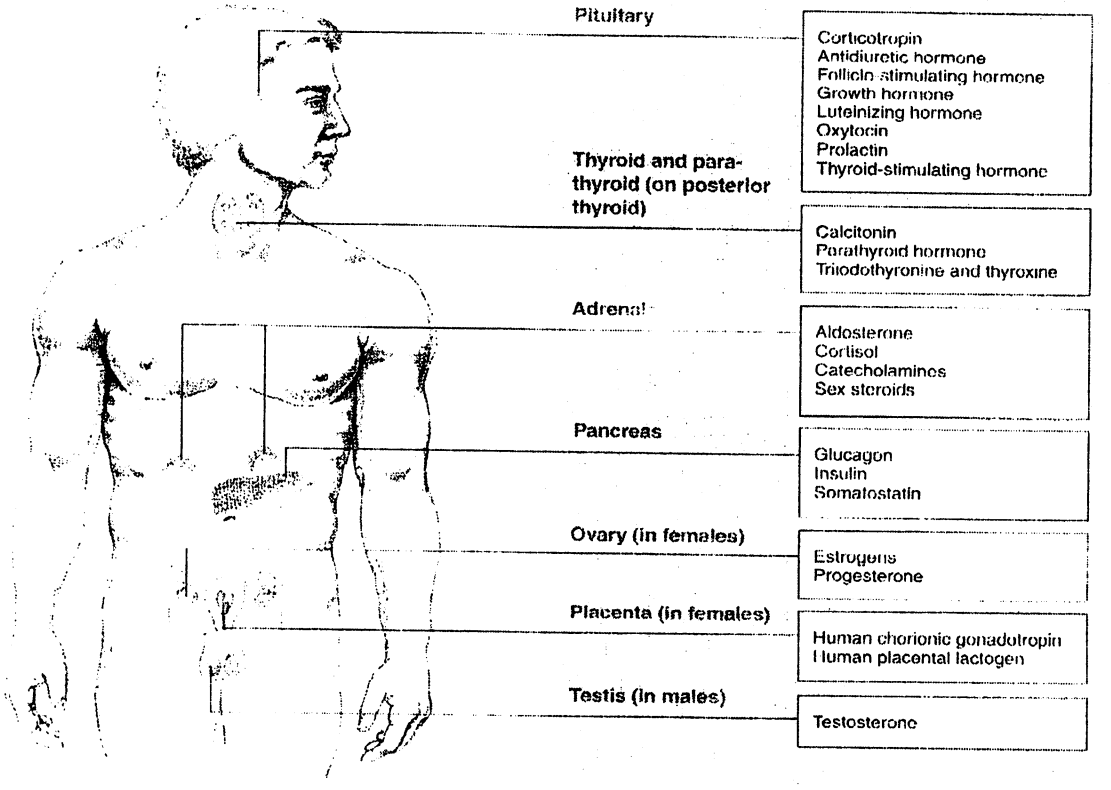
* *Hydrochloretic* = ↑ Water in bile e.g. Salicylates & Dehydrocholic acid.

NB) Cholagogues & Choleretics:
1- **Useful in**:
a- Flatulence b- Constipation c- Indigestion
d- Help absorption of fat & fat soluble vitamins.
2- **Contraindications**: a- Obstructive jaundice b- Acute hepatitis

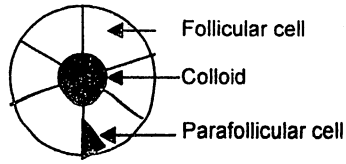
* *Chenodesoxycholic acid* *(Chenisolve)* & *Ursodeoxycholic acid* *(Ursofalk)*:
1- Useful in cholesterol stones → Dissolution of gall bladder stones.
2- ↓ Hepatic synthesis of cholesterol → ↓ Cholesterol in bile.
3- May cause diarrhea.

* *Heptotoxic Drugs;*
1- *Zonal (Centrilobular) Necrosis*: CCl_4 & Paracetamol.
2- *Viral Hepatitis-like*: Isoniazide, Phenytoin & Halothane.
3- *Chronic hepatitis*: Isoniazide, Phenytoin & α-Methyldopa.
4- *Cholestasis*: Methyl-testosterone, Oral Contraceptives, Carbimazole (Anti-thyroid), Chlorpropamide (Oral hypoglycemic), Chlorpromazine (Major tranquilizer) & Erythromycin (Antibiotic).
5- *Fatty liver*: Tetracyclines (Antibiotic) & Valproic acid (Anti-epileptic).

Hormones



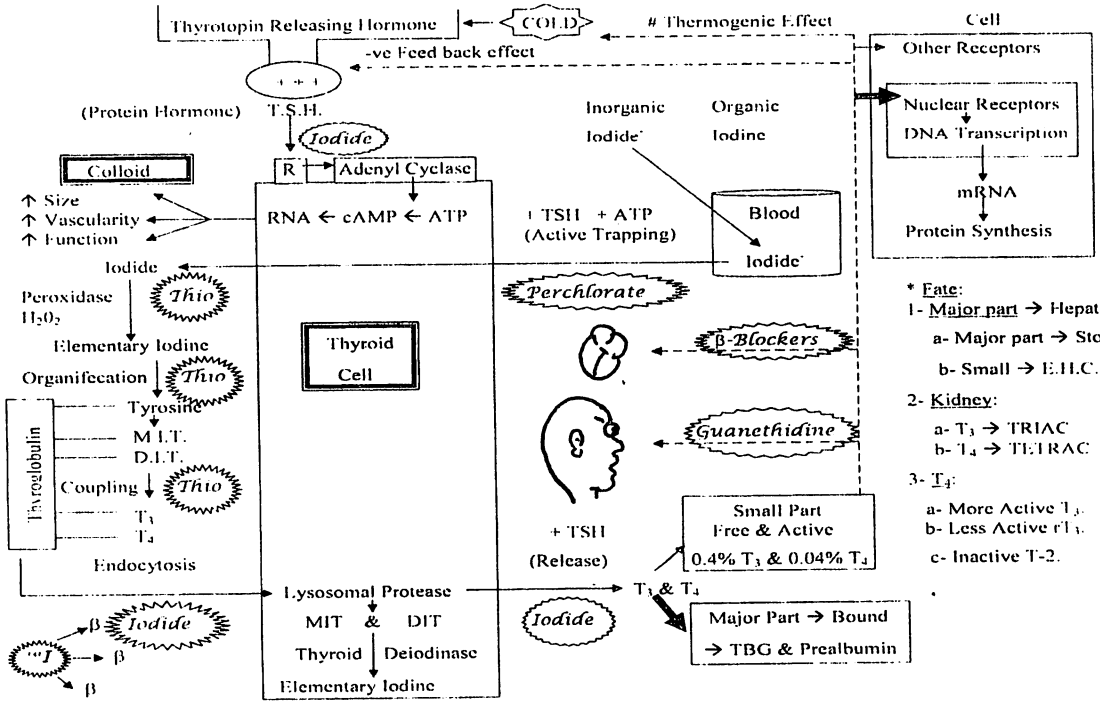
Thyroid Gland



Thyroid gland secretes 2 types of hormones:

1- Follicular cells → Thyroid hormones → ***Thyroxin*** (T_4) & ***Tri-iodothyronine*** (T_3).
2- Para-follicular cells (C-cells) → ***Calcitonin***.

* Synthesis, Storage & Release of Thyroid Hormones (T_4 & T_3):



1- Thyroid function starts early in *fetal life*, about the 3rd month.
2- Exposure to ***Cold*** ↑ *Hypothalamus* to secrete *Thyrotropin Releasing Hormone* (TRH).
3- **T.R.H.** ↑ *Anterior Pituitary* to secrete *Thyroid Stimulating Hormone* (TSH = Thyrotropin).
TRH ↑ membrane receptor linked to G-protein → ↑ PLC → ↑ DAG & IP_3 → ↑ Ca^{2+}.
4- **T.S.H.** (a glycoprotein) ↑ Thyroid gland → ↑ Size, Vascularity & Function.
TSH ↑ membrane receptor linked to G_S-protein → ↑ Adenylate cyclase → ↑ cAMP.

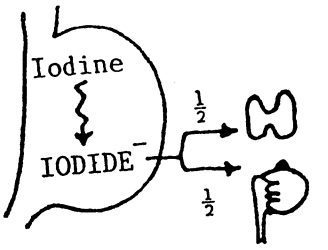
> ***NB) Long Acting Thyroid Stimulator (LATS) = Thyroid stimulating Immunoglobulin (TSI) → Immunoglobulin secreted by lymphocytes → Similar actions to TSH BUT:***
> ***1- NOT controlled by anterior pituitary.***
> ***2- No –ve feed back by circulating thyroid hormones.***
> ***3- Responsible for some cases of Hyperthyroidism (Graves disease).***

5- Active uptake & concentration of Inorganic Iodide⁻ = **Trapping** by thyroid cells via *Na/I symport*, under the effect of *TSH & ATP*.
About 50% of circulating Iodide⁻ is trapped by thyroid gland.

> NB) Active Trapping of Iodide⁻ can be **Inhibited** by:
> 1- Mono-valent chemical groups e.g. Perchlorate⁻, Thiocyanate⁻ & Nitrate⁻ → Compete with I^-.
> 2- Anaerobic conditions → Depletion of ATP.
> 3- Di-Nitro-Phenol → Uncoupling of Oxidative-Phosphorylation → ↓ ATP synthesis.
> 4- Digitalis e.g. Ouabain → ↓ ATPase → ↓ Utilization of ATP.

NB) Iodine Metabolism:

1- Food contains mainly Organic iodine → Not absorbed from GIT.
2- In GIT, organic iodine → Inorganic iodide⁻ → Absorbed.
3- About 50% of circulating Iodide⁻ is trapped by thyroid cells.
4- The remaining 50% of iodide is excreted mainly in urine.



6- Conversion of Inorganic Iodide⁻ → *Active ionic (elementary) Iodine* by peroxidase enzyme which catalyses H_2O_2.
7- **Organification** of Iodine = Iodination of Tyrosine: Ionic iodine combines with tyrosyl residue of colloidal thyroglobulin → 3-Mono- & 3,5-Di- iodo-tyrosines (MIT & DIT).

NB) *Thyroglobulin Is synthesized inside the thyroid cells to be stored outside cells in the colloid. It carries 115 tyrosine residues.*

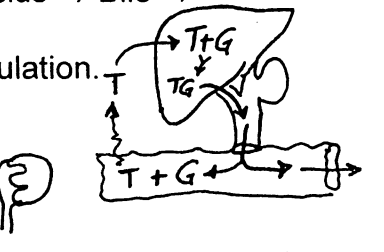
8- **Coupling** of MIT & DIT (catalyzed by peroxidase enzyme) → 3,5,3`-Tri-iodothronine (T_3) & Tetra-iodo-thyronine (Thyroxin, T_4) → Attached to thyroglobulin.

NB) Normal thyroid synthesize $T_3 : T_4 = 1 : 5$.
1- In iodine deficiency → More MIT → More T_3 → More potent than T_4.
2- In excess iodine → More DIT → More T_4 → Less potent than T_3.

9- **Storage** of thyroglobulin (attached to it MIT, DIT, T_3 & T_4) extra-cellularly in the colloid of the thyroid follicles.
10- **Endocytosis** of a drop of thyroglobulin under effect of TSH.
11- **Proteolysis** of thyroglobulin by Lysosomal enzymes.
12- **Release** of T_3 & T_4 under the effect of TSH.
13- MIT & DIT are inactive → retained inside thyroid cells → Deiodination by *Thyroid deiodinase enzyme* → Ionic iodine → Re-cycled in organification.
NB) Congenital deficiency of thyroid deiodinase → ↓ Available ionic iodine → Hypothyroidism.

* Kinetics of Thyroid Hormones:

1- *Absorbed* orally (T_3 → 95% & T_4 → 65%) → Better given before meals.
2- *Distributed* allover the body.
3- The major part of circulating T_3 (99.6%) & T_4 (99.96%) are *bound* to plasma proteins mainly *Thyroxin Binding Globulin* (TBG) & to less extent to prealbulin & albumin.
Only small fraction of T_3 (0.4%) & T_4 (0.04%) are free & active.
a- Estrogens (Pregnancy & oral contraceptives) → ↑ TBG.
b- Androgens & Cortisol → ↓ TBG.
c- Hypoproteinemia → ↓ Binding to T_3 & T_4.
d- Aspirin & Phenytoin → Displace T_3 & T_4 from their binding sites.
4- *Fate* of Thyroid hormones:
a- *Major* part → Hepatic *conjugation* with Glucuronic & Sulfuric acids → Bile →
- Major part is excreted in stool
- Some → Deconjugated → Absorbed → Entero-Hepatic circulation.



b- In Kidney & Liver → *Oxidative deamination & transamination*:
- T_3 → Tri-Iodo-Thyro-Acetic acid (TRIAC) → Urine.
- T_4 → Tetra-Iodo-Thyro-Acetic acid (TETRAC) → Urine.

c- ***T_4 → Peripheral deiodination*** →
- T_4 (Prohormone) → More active T_3 (3, 5, 3` T_3 → 4 X T_4) = 80% of T_3 in the body. This can be inhibited by Propylthiouracil, Propranolol & cortisol.
- Less active reverse T_3 (3, 3`, 5` T_3 = rT_3 = 1/10 T_4 = Partial agonist).
- Inactive 3, 3` Di-iodothyronine.

	Thyroxin (T=4)	Tri-iodo-thyronine (T_3)
1- Origin	100% Thyroid	20% Thyroid + 80% deiodination of T_4
2- Potency	1= (Pro-hormone)	4
3- Oral bioavailability	65%	95%
4- Biological lag	24 hours	6 hours
5- Half life	7 days	1 day
6- Bound form	99.96%	99.6%
7- Free form	0.04%	0.4%
8- Serum level ug/ml	5 – 11	0.1 – 0.2

*Mechanism of Action of Thyroid Hormones:

1- Thyroid hormones → Lipophilic → gain access intra-cellularly by passive diffusion.
2- *Genomic mechanism* → Bind to Nuclear receptors → DNA transcription → mRNA → Cytoplasm → Ribosomes → Protein synthesis → Usually active metabolic enzymes. This action needs hours to be manifested = Biological lag.
3- *Non-genomic mechanisms* → Thyroid hormones bind also to other receptors e.g. Cell membrane & mitochondria.

*Actions of Thyroid Hormones:

1- *-ve feed back* effect on hypothalamic TRH & pituitary TSH.
2- *Calorigenic (Thermogenic)* effect due to uncoupling of oxidative phosphorylation → ↑ O_2 consumption, heat production & B.M.R.
3- *Supersensitivity* to BOTH Sympathetic & Parasympathetic.
4- *C. V. S.*:
   a- Direct action on heart & B.V. → V.D. & ↑ Heart.
   b- Supersensitive α & β receptors → V.C. & ↑ Heart.
5- *Kidney* → Diuretic effect.
6- *G. I. T.* → ↑ Motility (Direct effect & Supersensitive parasympathetic).
7- *Metabolic actions*:
   a- Carbohydrate → ↑ Intestinal absorption of glucose & ↑ its tissue utilization.
   b- Fat → lipolysis.
   c- Hypocholesterolemic (Especially synthetic d-thyroxin): ↑ Conversion of cholesterol to bile acids.
   d- Proteins → Catabolic.
   e- Bone → Osteoporosis → Mobilization of Calcium → Hypercalcemia & Hypercalcuria.
8- *Essential* for physical growth, mental development & sexual maturation.

NB) Manifestations of Hypothyroidism:
1- Children → Cretinism → Stunted growth + Apathy
2- Adults → Myxedema +
   a- Apathy & lethargy
   b- Intolerance to cold
   c- Bradycardia
   d- Constipation
   e- Hypercholesterolemia
   f- Infertility.

NB) Manifestations of Hyperthyroidism = Toxicity of Thyroid hormones:

1- Exophthalmos:
- *a- ↑Sympathetic activity → ↑Levator palpebri superiosis & retrobulbar (Muller's) muscle.*
- *b- ↑Exophthalmos producing factor → Deposition of tissues in the orbit behind eye ball.*

2- Intolerance to heat, hyperpyrexia, warmness & flush.

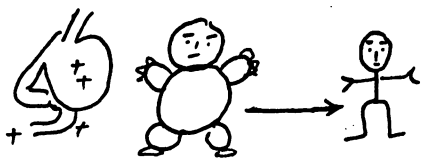
3- ↑Sympathetic activity → Anxiety, tremors, sweating & Exophthalmos.

4- C.V.S. → Peripheral V.D., Marked Tachycardia, ↑COP, ↑Cardiac work → Angina, Arrhythmia & Hypertension (↑Systolic but ↓Diastolic) → Cause of Death.
Thyroid hormones are contraindicated in Ischemic heart disease & Heart failure.

5- Kidney → Diuresis.

6- G.I.T. → ↑Motility → Diarrhea → Mal-absorption.

7- Metabolic:
- *a- ↑Appetite BUT weight loss due to ↑Metabolic rates.*
- *b- Hyperglycemia → ↑Absorption, Glycogenolysis (depletion of hepatic glycogen) & gluconeogenesis.*
- *c- Lipolysis*
- *d- Catabolic → -ve Nitrogen balance*
- *e- Osteoporosis, Hypercalcemia & Hypercalcuria.*



*Preparations & Daily Requirements of Thyroid Hormones:

1- *Levo-Thyroxin sodium* (l-Thyroxin, T_4): 100 ug/day Oral & Parenteral.
Slow onset & Long duration → Useful orally in Cretinism & Myxoedema.

2- *Liothyronine sodium* (l-T_3}: 25 ug/day Oral & Parenteral
Potent & Rapid onset → Useful I.V. in Myxoedema coma

3- *Liotrix*: $T_4 + T_3 \rightarrow 4 : 1$ similar to normal physiological ratio

4- *d-Thyroxin* → Synthetic → Hypocholesterolemic *But Not* replacement therapy.

*Therapeutic Uses of Thyroid Hormones:

1- *Replacement* therapy in *Hypothyroidism*:

* *Types of Hypothyroidism:*

a- *Primary:*
- *Due defect in thyroid gland itself e.g. Inflammation (Hashimoto's disease), surgical removal, over dose of anti-thyroid drugs e.g. Radio-active Iodine.*
- *Low serum thyroid hormones **BUT** high TSH.*

b- *Secondary to Hypothalamo-pituitary defect → LOW Both Thyroid hormones & TSH.*

* *Treatment of Hypothyroidism:*

Therapy is monitored by frequent determination of circulating T_3, T_4 & TSH by radio-immuno assay (RIA) and clinical response of the patient.

a- Myxoedema: Oral Levo-thyroxin sodium
Start by 50 ug/day for 2 weeks, ***IF*** inadequate → 100 ug/day for 2 weeks,
IF inadequate → 150 ug/day for life.

b- Myxoedema coma: Liothyronine sodium 25 ug I.V. / 6 hours.

c- Cretinism: Levo-thyroxin sodium as early as possible,
Age < 6 months → 10 ug / kg → From 6 – 12 months → 8 ug / kg
From 1 – 5 years → 6 ug / kg → From 5 – 10 years → 4 ug / kg
More > 10 years → Adult dose

2- Simple Non-Toxic goiter (Non-functioning): Usually due to iodine deficiency → ↓ Thyroid hormones → ↑ TSH → ↑ Size of thyroid gland.
3- Thyrotropin (TSH) – Dependent cancer thyroid.
4- Constipation if due to hypothyroidism
5- Infertility, Amenorrhea & habitual abortion if due to hypothyroidism
6- Hypercholesterolemia:
   a- In hypothyroid patient → Use L-Thyroxin → Replacement therapy.
   b- In euthyroid patient → Use d-Thyroxin → Hypocholesterolemic ONLY.

Treatment of Hyperthyroidism

A) Antithyroid Drugs:
1- **Thioamides**: They ↓ Organification → ↓ Synthesis of thyroid hormones.
2- **Ionic Inhibitor** e.g. **K^+ Perchlorate** → ↓ Trapping of $Iodide^-$ → ↓ Synthesis of T_3 & T_4.
3- **Iodide Therapy** e.g. Lugol's iodine → Attenuates effect of TSH.
4- **Radioactive ^{131}Iodide** → Emits β-rays → Destroy thyroid tissue.

B) Sympathetic Depressants → Control Peripheral Manifestations:
1- **β-Blockers** e.g. Propranolol → Cardio-protective.
2- **Guanethidine** eye drops → ↓ Exophthalmos.

C) Surgical: Subtotal thyroidectomy.

I- Thioamides (Thiouracils , Thioureas):

* Preparations:

1- **Propylthiouracil**: 100 mg tds till control of symptoms (4-8 weeks) then 50 mg od po.
2- **Methimazole**: 10 mg tds till control of symptoms (4-8 weeks) then 5 mg od po.
3- **Carbimazole**: Similar to Methimazole.

* Pharmacokinetics:

1- Well absorbed from GIT.
2- Distributed all over the body. Concentrated in thyroid gland.
   Passes BBB. Passes placental barrier → ↓ Fetal thyroid gland.
3- In liver, **Carbimazole (prodrug) → Methimazole (active metabolite).**
4- Excreted in urine. Excreted in milk → Affects suckling babies.

* Mechanism of Action of Thioamides:

1- *They **↓ Organification** of $iodide^-$ → **↓ Synthesis** of thyroid hormones.*
2- ↓ Peroxidase enzyme → ↓ conversion of $Iodide^-$ to Elementary iodine.
3- ↓ Iodination of tyrosyl residues of thyroglobulin → ↓ Synthesis of MIT & DIT
4- ↓ Coupling of Iodotyrosines (MIT & DIT) → ↓ Synthesis of Iodothyronines (T_3 & T_4).
5- Propylthiouracil, in addition, ↓ Peripheral deiodination of T_4 to T_3.

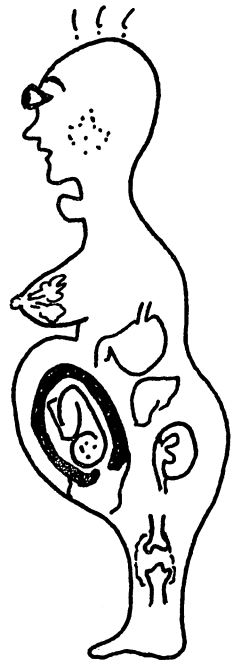
* Effects of Thioamides:

1- ↓ Thyroid function after a latent period (1-3 weeks), till depletion of stored colloid.
2- ↑ Size & vascularity of thyroid gland due to ↑ TSH release.
If thyroidectomy to be done, use Iodide therapy 7-10 days before operation to ↓ size and vascularity of the thyroid gland.
3- ↑ Exophthalmos, may be due to ↑ release of Exophthalmos Producing Factor.

* Therapeutic uses of Thioamides:

1- Drug of CHOICE in treatment of MILD hyperthyroidism.
Moderate & severe hyperthyroidism are treated surgically or by radioactive ^{131}I.
2- Temporary control in moderate & severe hyperthyroidism till:
a- Preparation of the patient for subtotal thyroidectomy.
b- Appearance of effects of radioactive ^{131}I (3 months).
3- Propylthiouracil may be used in control of hyperthyroid crisis (storm).

* Side Effects & Toxicity of Thioamides:



1- ***AGRANULOCYTOSIS***:
a- Patients should be aware of any infection e.g. sore throat or fever.
b- Frequent blood count may be needed.
c- If it occurs → Stop the drug & Prompt treatment (see blood).
2- ALLERGY: Skin rash & fever.
3- ↑ Size & vascularity of thyroid → Difficult to operate upon.
4- Exophthalmos.
5- During pregnancy & lactation → Cretinism.
6- Loss or depigmentation of hair.
7- GIT disturbances.
8- Liver & kidney damage.
Carbimazole → Cholestatic jaundice.
9- joint pains.

II- Potassium Perchlorate

1- Mechanism of Action : **Ionic Inhibitor** → Competes with $Iodide^-$ for uptake & storage by thyroid gland → ↓ Trapping → ↓ Synthesis of Thyroid hormones (T_3 & T_4).

2- Effects → Similar to Thioamides.

3- Therapeutic Uses:
a- Similar to Thioamides. It is used to substitute Thioamides in patients allergic to them.
b- Test of organification. Estimate discharged $iodide^-$ from thyroid gland.

4- Side Effects & Toxicity → Similar to Thioamides, in addition:
a- Fatal APLASTIC anemia.
b- Concurrent use of $Iodide^-$ → Hyperthyroid crisis.

III- Iodide Therapy

* Preparations:

1- **Lugol's iodine** (5% iodine in 10% potassium iodide) : 0.3 ml (10 drops) tds orally.
2- **Potassium Iodide**: 60 mg tds orally.

* Actions of Iodides:

A) Antithyroid Effect :

1- Attenuate effect of TSH on cAMP.
2- ↓ Size & vascularity of thyroid gland.
3- ↓ Endocytosis of colloid (thyroglobulin) → Colloid accumulates in the follicle lumen.
4- ↓ Proteolysis of thyroglobulin.
5- ↓ Release of T_3 & T_4.
6- ↑ Release of TSH.
7- The Antithyroid effect:
   a- Appears rapidly, within 24 hours, after administration as if thyroidectomy.
   b- Maintained for 10-15 days, then Relapse of hyperthyroidism due to ↑ TSH level = Paradoxical effect of iodide therapy.

B) Saline Expectorant *(see respiration).*

* Therapeutic Uses of Iodides:

1- Pre-operative (7-10 days) preparation before subtotal thyroidectomy.
2- Hyperthyroid crisis (Na or K iodide IV).
3- Saline Expectorant in chronic bronchitis (see respiration).

* Side Effects, Toxicity & Contraindications: *(see respiration)*

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IV- Radioactive ^{131}Iodide

* Mechanism of Action:

1- Radioactive ^{131}Iodide is Trapped by thyroid gland.
2- ↑ Trapping of ^{131}I by ↑ TSH:
   a- Inject TSH.
   b- ↓ Circulating T_3 & T_4 e.g. Antithyroid drugs, thyroidectomy or radiation of thyroid gland → ↑ TSH → ↑ Uptake by metastatic thyroid tissue.
3- In thyroid gland: Radioactive ^{131}I → Radioactive T_3 & T_4.
4- Radioactive T_3 & T_4 are stored in the colloid.
5- Radioactive ^{131}I emits 2 types of radiations:
   a- ^{131}I in large dose → β-rays → Destructive & of Low penetration (0.5 mm).
   b- ^{131}I in small dose → Gamma-rays → Non-destructive but of High penetration.

* Therapeutic uses of ^{131}Iodide:

1- **Hyperthyroidism**; Moderate to severe cases in:

a- Old age & Cardiac disease → Patient is unfit for surgery.
b- Recurrence after subtotal thyroidectomy.
c- Failure of Antithyroid drug therapy.

> * *Treatment Schedule:*
> *1- Dose: 80-150 microcuries / gram thyroid. Small doses are preferred.*
> *2- Aqueous solution of Na ^{131}Iodide either Orally (solution or capsule) or IV.*
> *3- Most of patients respond to Single administration.*
> *4- The effect of treatment by radioactive iodide appears after 2-3 months, during which, patient is temporary controlled by Antithyroid drug + β-blocker.*

2- Cancer thyroid.

3- Test the function of thyroid. Use small trace dose of ^{132}I, then measure Gamma-rays.

> NB) 1- ^{131}I $t_{1/2}$ = 8 Days → Used mainly for Therapy.
> 2- ^{132}I $t_{1/2}$ = 2 Hours → Used mainly for Diagnosis.

* Side Effects of Radioactive Iodide:

1- Local pain & congestion at site of thyroid gland.
2- Hypothyroidism.
3- Malignant changes in thyroid after many years.

* Contraindications of Radioactive Iodide:

1- Young patients < 30 years → Hypothyroidism & high chance for malignancy.
2- During Pregnancy (after 3rd month) → Damage of fetal thyroid.

V- β - Blockers

1- ***Example***: Propranolol (Oral & IV).
2- ***Advantages***:
   a- NO I.S.A.
   b- Protects the Heart from tachycardia, angina & arrhythmia of hyperthyroidism.
   c- Passes BBB → ↓ Anxiety & tremors of hyperthyroidism.
   d- ↓ Conversion of T_4 to the more active T_3.
3- ***Use***:
   a- Orally in Temporary relief of manifestations till control of hyperthyroidism by Antithyroid drugs or Thyroidectomy or Radioactive Iodide.
   b- IV in Emergency treatment of hyperthyroid crisis.

VI- Guanethidine

Eye drops → ↓ Exophthalmos by relaxing sympathetically innervated smooth muscles that cause eye lid retraction. Corticosteroids & surgical decompression may be needed.

Choice of Treatment of Hyperthyroidism

I- Mild Hyperthyroidism :

1- *Antithyroid* drug (Thioamide or K Perchlorate) Orally. Try for a year.
2- *Anti-anxiety* e.g. Barbiturates or Benzodiazepines.
3- *Propranolol* Orally.
4- *Guanethidine* Eye Drops.

II- Moderate & Severe Hyperthyroidism:

A) Surgical Treatment → Subtotal Thyroidectomy

1- Preparation for Surgery:

a- *Sedatives & tranquilizers* e.g. Diazepam or Phenobarbitone.
b- *Propranolol*, resting heart rate should be < 90 b/min.
c- *Antithyroid* drugs (Thioamides or K Perchlorate) for 4-8 weeks. Stop 10-14 days before the operation.
d- *Lugol's iodine* or K I is used 7-10 days before the operation.

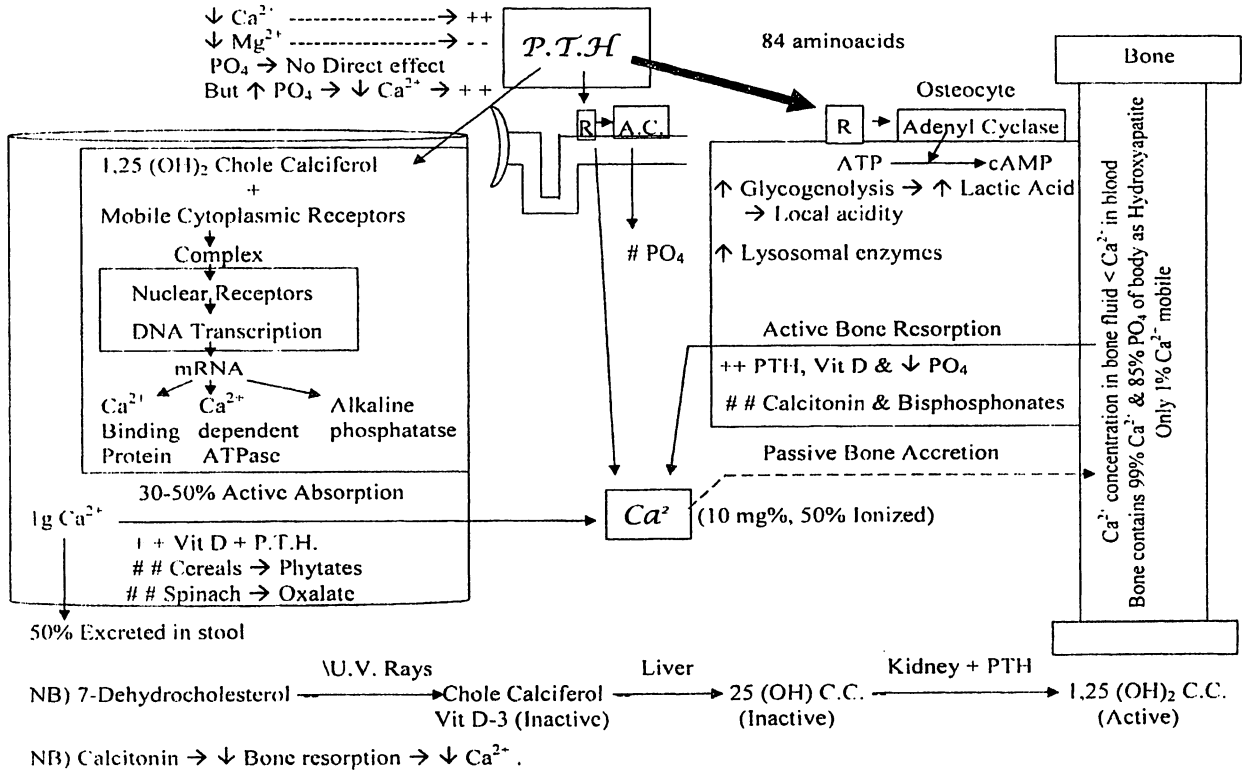
2- Treatment of Thyroid Crisis or Storm after the Operation:

a- *I.V. Fluids* e.g. Dextrose ± Electrolytes.
b- *Sodium Iodide* (250 mg/6 H Orally or IV) → ↓ Release of Thyroid hormones.
c- *Propylthiouracil* (250 mg/6 H Orally) → ↓ Conversion of T_4 to T_3. & ↓ their synthesis.
d- *Propranolol* (1-2 mg Slow IV or 40-80 mg/6 H Orally) → Cardio-protection & ↓ conversion of T_4 to T_3.
e- *Hydrocortisone hemisuccinate* (50-100 mg/6 H IV) → Anti-shock & # T_4 → T_3.
f- *Treatment of Hyperpyrexia*. Ice packs, sponges with cold water & alcohol.

B) Radioactive ^{131}Iodide:

1- Dose: 80-150 microcuries / gram thyroid. Small doses are preferred.
2- Aqueous solution of Na ^{131}Iodide either Orally (solution or capsule) or IV.
3- Most of patients respond to Single administration.
4- The effect of treatment by radioactive iodide appears after 2-3 months, during which, patient is temporary controlled by Anti-thyroid drug + β-blocker.

Calcium Metabolism



1- **Blood level of calcium** is 9 – 11 mg / 100 ml. About 50% is ionized.
Ionized Ca^{2+} has important physiological role e.g. blood coagulation.

2- **Solubility constant** = Ca^{2+} X PO_4 = Constant.
Plasma level of Ca^{2+} is *Inversely* proportional to phosphate level.

3- **Bones** contain about 99% of Ca^{2+} & 85% of phosphorus in the body mainly as crystalline Hydroxyapatite [$Ca_{10}(PO_4)_6(OH)_2$].
Only 1% of this Ca^{2+} is mobile (exchangeable).

4- Ca^{2+} concentration in plasma > its concentration in bone fluid.

5- **Bone Accretion** = Passive passage of Ca^{2+} from blood to bone fluid.

6- **Bone Resorption** = Active passage of Ca^{2+} from bone fluid to blood.

7- **Osteocytes**:
a- Osteoblast → Bone forming,
b- Osteoclast → Bone resorbing.

8- **Kidney** → Active Ca^{2+} & Phosphate reabsorption.

9- **Upper intestine** → Active Ca^{2+} absorption about 30-80% of dietary Ca^{2+}.
a- ↑ Absorption by Vit D & Parathyroid hormone.
b- ↓ Absorption by Phytic acid & oxalic acid.

10- **Control** of Ca^{2+} level in blood:
a- Mainly: Parathyroid hormone, Vit D & Calcitonin.
b- Others: Growth hormone, Thyroid hormones, corticosteroids, sex hormones & Drugs.

Parathyroid Hormone (Parathormone, PTH)

*Nature & Source:

1- Single polypeptide hormone (84 aminoacids) derived from prohormone (90 aminoacids).
2- Synthesized, stored & secreted by Parathyroid glands.

*Control of Release of PTH:

1- Low blood Ca^{2+} → ↑ Release.
2- Low blood Mg^{2+} → ↓ Release.
3- High Blood Phosphate → Low blood Ca^{2+} → ↑ Release = Indirect effect.

*Pharmacodynamics of P.T.H.:

1- Mechanism of Action:
P.T.H. ↑ membrane receptor linked to G_S-protein → ↑ Adenylate cyclase → ↑ cAMP.

2- ↑ Ca^{2+} Level in Blood:
a- ↑ Osteoclastic activity → **Active bone Resoprtion**:
- ↑ Glycogenolysis → ↑ Lactic acid → ↑ Acidity → Solublize Ca^{2+}.
- ↑ Lysosomal activity → Bone digestion → Mobilize Ca^{2+}.

b- ↑ Ca^{2+} & ↓ Phosphate **Active Reabsorption** from the kidney.
c- ↑ Active Ca^{2+} **Absorption** from GIT by activation of Vit D.

3- Therapeutic Uses:
I.M. injection. Repeated use → Antibody formation → Tolerance.
a- Hypocalcemia & Tetany.
b- Intermittent use of small dose of PTH is useful in treatment of osteoporosis **(Paradoxically ↑ bone formation by an unknown mechanism).**

Vitamin D

1- Types:
a- Vitamin D-2 = Ergo-Calciferol of plant origin.
b- Vitamin D-3 = Cholecalciferol in higher mammals.

2- Steroid vitamin → Effective orally & acts intra-cellulary.

3- Skin 7-Dehydro-**Cholesterol** $\xrightarrow{\text{U.V. Ray}}$ **Cholecalciferol** (Inactive) $\xrightarrow{\text{Liver 25 Hydroxylase}}$
25 Hydroxy-Cholecalciferol (**Calcifediol**, Inactive) $\xrightarrow{\text{Kidney 1-}\alpha\text{-Hydroxylase ++ PTH}}$
1-α, 25 Dihydroxy-Cholecalciferol (**Calcitriol**, ***Active***).
In Renal disease → No 1-α hydroxylation of Vitamin D → Renal Rickets.

4- Vitamin D → **↑ Ca^{2+} in blood**:
   a- **↑ Active intestinal Absorption**.
      Calcitriol passes inside intestinal mucosa passively → Bind to cytoplasmic receptor (carrier) → Mobile complex → Nucleus → ↑ Nuclear receptor → DNA transcription → mRNA → Cytoplasm → Protein synthesis → Ca^{2+}-Binding protein, Ca^{2+}-dependent ATPase & Alkaline phosphatase.
   b- ↑ Active bone Resorption.
   c- Weak ↑ Active Ca^{2+} absorption from the kidney.

5- **Anti-Rickets effect** → Maturation & calcification of epiphyseal cartilage.

6- **Useful** Orally & Parenterally in:
   a- Hypocalcemia & Tetany.
   b- Rickets & Osteomalacia e.g. with long use of anti-epileptic drugs.

6- **Preparations**:
   a- **Ergocalciferol** (Vitamin D-2) oral capsules (50'000 U) & I.M. injection (600'000 U).
   b- **Cholecalciferol**: Halbut & Cod liver oil.
   c- **Alfacalcidol** (1-α-OH-Cholecalciferol).
   d- **Calcitriol** (1-α, 25 $(OH)_2$ Cholecalciferol).

Dihydrotachysterol (Anti-Tetanic 10, AT-10)

1- **Steroid** → Orally & acts intracellularly.
2- **Synthetic analogue** of Vitamin D-2 *BUT* → More Hypercalcemia & Less Anti-Rickets.
3- Used **Orally** in treatment of Hypocalcemia & Tetany.

Calcitonin (Thyrocalcitonin)

1- **Polypeptide** hormone → Not effective orally & acts on membrane receptors.
2- **Hypocalcemic** hormone. Synthesized, stored & secreted from thyroid parafollicular (C-Cells) in response to Hypercalcemia.
3- **↓ Bone Resorption** & ↓ Active renal reabsorption of Ca^{2+} & Phosphate.
4- Has an **Analgesic** effect.
5- Therapeutic **Uses**:
   a- Hypercalcemia b- Paget's disease of bone.
   c- Post-menopausal osteoporosis ± Estrogen replacement therapy.
6- **Preparations**:
   a- Human calcitonin (Cibacalcin): I.M. & S.C.
   b- Salmon calcitonin (Miacalcic): I.M., S.C. & Nasal spray.

Bisphosphonates

1- **Examples**:
   a- **Alendronate** (Fosamax, 5-10 mg)
   b- **Disodium Clodronate** (Bonefos, 300-400 mg)
   c- **Disodium Pamidronate** (Aredia, 15 mg)
   d- **Risedronate Sodium** (Actonel, 5 – 35 mg)
2- **Synthetic** compounds → Apoptosis of **Osteoclasts** → ↓ Bone **Resorption** → **↓ Ca^{2+}**.
3- Effective **orally** & parenterally in the same indications of Calcitonin.

* Treatment of Osteoporosis:

1- **Bisphosphonates** e.g. Alendronate.
2- **Calitonin**.
3- **Estrogens** in Hormonal replacement Therapy (HRT) to prevent Post-menopausal osteoporosis.
4- **Raloxifene** → Selective Estrogen Receptor Modulator (SERM):
   a- Agonist on estrogen receptors in bone (↑ Osteoblast & ↓ Osteoclast) & C.V.S.
   b- Antagonist on estrogen receptors in mammary & uterus tissues.
5- Small doses of **Parathormone** given Intermittently → Paradoxically ↑ Osteoblast activity & ↓ Osteoclast activity → ↑ Bone formation.
6- **Vitamin D**
7- **Calcium** salts e.g. Calcium gluconate.
8- **Fluoride**
9- **Statins** (HMG-CoA-Reductase Inhibitors → Hypocholesterolemic agents).

*Treatment of Hypercalcemia:

1- **Calcitonin** Injection
2- **Bisphosphonates** orally.
3- **Phosphate** injection → ↑ Blood phosphate → ↓ Bone Resorption → ↓ Ca^{2+} in blood.
4- **Glucocorticoids** e.g. Cortisol → Anti-Vitamin D → ↓ Ca^{2+} Absorption.
5- **Loop** diuretics (↑Ca^{2+} in urine) & *Avoid* thiazide diuretics.
6- **Sodium Edetate** → Chelating agent.
7- **Mithramycin** (Plicamycin): Cytotoxic antibiotic → ↓ Bone Resorption.
8- **Dialysis**.

*Treatment of Hypoparathyroidism = Hypocalcemia = Tetany.

↓ PTH → ↓ Ca^{2+} (if < 7 mg% → Tetany) & ↑ Phosphate.

A) Acute Tetany:

1- **Calcium Gluconate** 10 ml 10% Very Slow I.V. then I.M. & Oral.
2- **Parathoromone** I.M.

B) Chronic Hypoparathyroidism: Aim → ↑ Ca^{2+} in blood.

1- ***D***iet rich in Ca^{2+} & Poor in Phosphate e.g. Milk & Dairy products.
2- Vitamin ***D*** Orally: Ergocalciferol, Cholecaliferol, Alfacalcidol & Calcitriol.
3- ***D***ihydrotachysterol (AT-10) Orally.
4- Thiazide ***D***iuretics.
5- Oral ***A***luminum hydroxide → ↓ Oral absorption of phosphate → ↓ PO_4 → ↑ Ca^{2+}.
6- ***A***cidifying agents e.g. ***A***mmonium chloride → ↑ Solubility constant.
7- ***A***void ***A***lkalosis e.g. Sodium bicarbonate & Aspirin L.D. → Respiratory alkalosis.

*Hyperparathyroidism:

1- **Primary** due to PTH secreting adenoma → Treat by Surgery of Deep X-ray.
2- **Secondary** due to chronic hypocalcemia e.g. Renal failure → Treat by ↑ Ca^{2+}.

Pancreatic Hormones

Insulin

1-The pancreas contains about one million (1000'000) islets of Langerhans.

2-Each islet contains four types of polypeptide hormone-producing cells:

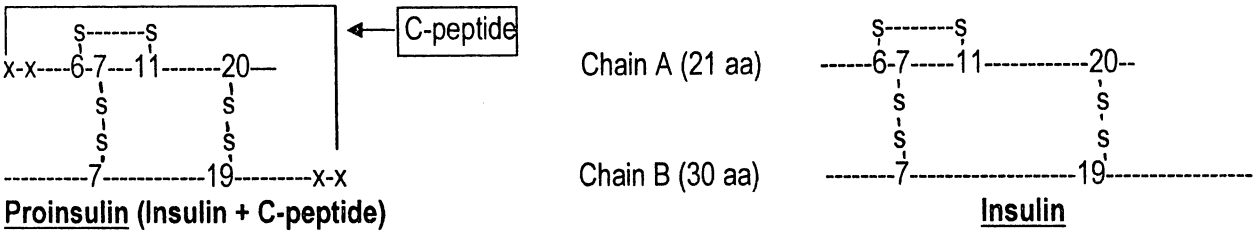
a-A "α" Cells (20%) → Glucagon → Counter-insulin → Hyperglycemia.
b-B "β" Cells (75%) → Insulin → Synthesis & Storage.
c-D "δ" Cells (3-5%) → Somatostatin → ↓ A cells > ↓ B cells → ↓ Glucagon > ↓ Insulin
d-F "PP" Cells (2%) → Pancreatic Polypeptide → ↑ Digestive process.

N.B.) Glucagon:

1- Single chain polypeptide of 21 amino-acids.
2- Synthesized, stored & released from α-cells of Islets of Langerhans & from Upper GIT:
   a- Plasma: ↓ Glucose & ↓ Fatty acids or ↑ Amino-acids e.g. L-Arginine → ↑ Release.
   b- Autonomic: β_2 & M → ↑ Release.
   c- Insulin & Somatostatin → ↓ Release
3- ↑ Specific membrane receptors → ↑ Adenylate cyclase → ↑ cAMP:
   a- ↑ Glycogenolysis & Gluconeogenesis (in liver Not skeletal muscle) → ↑ Glucose
      ↑ Lipolysis & Catabolic (skeletal muscle) → Counter regulatory to insulin
      Useful SC & IM in treatment of Hypoglycemic coma when IV Glucose is not available.
   b- ↑ Heart → +ve Ino & +ve Chrono → Useful in heart failure induced by β-blockers.
   c- Smooth muscle relaxation → Useful before radiological examination.

* Synthesis, Storage & Release of Insulin:

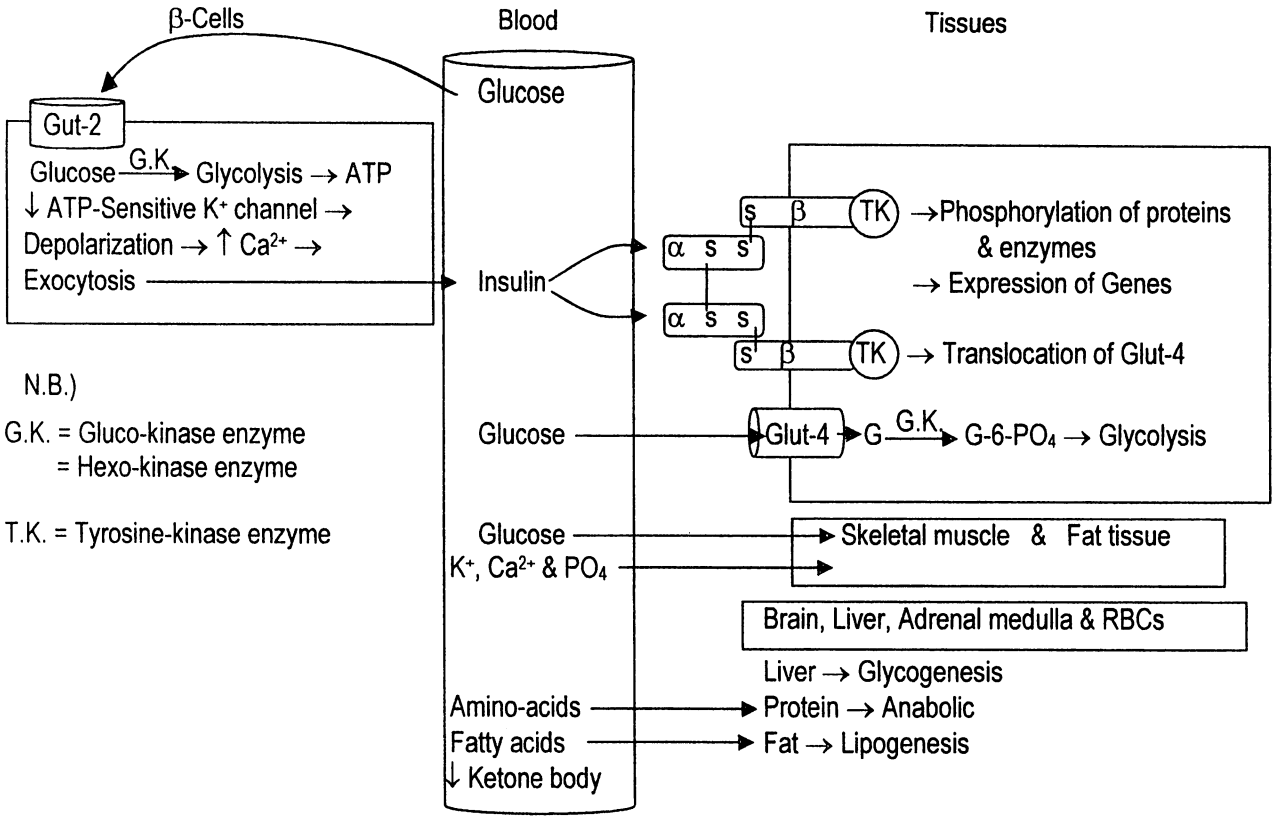
1- Insulin is ***synthesized*** in β-cells of pancreatic islets of Langerhans as a single chain proinsulin → Insulin + C-peptide (Single chain 31 aa). Insulin is a double chain polypeptide of 51 aa (chain A 21 aa & chain B 30 aa) connected together by 2 bisulphide bridges. The integrity of these bridges is essential for activity. A third bridge within chain A.



Proinsulin (Insulin + C-peptide) **Insulin**

2- Insulin is ***stored*** in specific granules in β-cells.

3- β-cells also synthesize and store ***Amylin***.
   a- It is a single chain polypeptide of 37 aa. It is stored and released with insulin.
   b- Amylin → Delays gastric emptying, ↑ Sk.m. glycogenolysis & ↓ insulin release.
   c- ***Pramlintide*** (Amylin analogue) → May be used with insulin in diabetes to →
      ↓ Gastric emptying → ↓ Postprandial hyperglycemia.



4- ***Release*** of insulin. High blood glucose enters β-cells by Glut –2 glucose transporter → Glucokinase (Hexokinase) → Glycolysis → Generation of ATP → Block of ATP-Sensitive K^+-channel → Depolarization → ↑ Voltage-gated Ca^{2+} → Influx of Ca^{+2} → Exocytosis of Insulin, C-peptide & Amylin.

5- Daily output of insulin = 30 – 40 U.

* Regulation of insulin Secretion:

1- FOOD → ↑ Release specially **GLUCOSE** is the most powerful, amino-acids (Leucin & Argining) & fatty acids.

2- GIT Hormones (Secretin, Gastrin, Gasrtic Inhibitory Peptide, VIP & CCK) →↑ Secretion.

3- Systemic Hormones:
   a- Glucagon & Growth hormone → ↑ Secretion.
   b- Somatostatin → ↓ Secretion, but ↓ Glucagon more.

4- PGE-1 → ↓ Secretion.

5- Autonomic Receptors:
   a- α-2 → ↓ cAMP → ↓ Secretion of insulin eg Adrenaline
   b- α-blockers → ↑ Release.
   c- β-2 → ↑ cAMP → ↑ Secretion of insulin
   d- β-blockers → ↓ Release.
   e- Muscarinic → ↑ IP-3 & DAG → ↑ Secretion of insulin.
   f- M-blockers → ↓ Release

6- Fasting & Starvation → Hypoglycemia → ↑ Sympathetic → Adrenaline & Noradrenaline → ↓ Release

7- Drugs: a-Sulphonylurea & analogues → ↑ Release of insulin.
   b-Thiazides, diazoxide. Phenytoin & verapamil → ↓ Release.

* Fate of Insulin:

1- NOT effective orally, used parenterally usually SC. In emergency diabetic coma soluble insulin can be given IM & IV.

2- Extensive hepatic first pass metabolism (50%), mainly by glutathione-insulin trans-hydrogenase (Insulinase) enzyme → Break bisulphide bridges → Inactivation.

3- Short t ½ of endogenous insulin = 5 minutes.

*Pharmacodynamics of Insulin:

A) Mechanism of Action:

1- Insulin binds to specific membrane receptors, each receptor has α & β subunits connected together by 2 bisulphide bridges. The α subunit is outside while the β is transmembrane and has a tyrosine kinase activity. Insulin binds to the α subunit → Activation of tyrosine kinase activity of β subunit → Phospholrylation of intracellular proteins → Change in enzyme activity, gene expression and translocation of Glut-4 transporter → Glucose uptake by adipose tissue & Sk.m.

2- Insulin → ↓ Adenylate cyclase → ↓ cAMP → Anti-glycogenolytic & Anti-lipolytic.

3-The insulin/receptor complex is then rapidly internalized into the cell → Metabolism of insulin and recycling of the receptor.

4- Glucagon, Growth hormone, Glucocorticoids, Thyroid hormones & Catcholamines antagonize the actions of insulin → Counter-regulators → Essential for glucostasis.

B) Actions of Insulin:

1- ***Carbohydrate***:
- a- **Hypoglycemia**: Insulin facilitate glucose uptake by adipose tissue and Sk.m.
  NB) Brain, liver, adrenal medulla, RBCs & WBCs have different glucose transport mechanisms.
- b-↑ Glugokinase (Hexokinase) enzyme → Glucose 6-Phosphate → ↑ Glucose utilization = ↑ Glycolysis.
- c-↑ Glycogenesis by ↑ Glycogen synthase
  BUT ↓ Glycogenolysis by ↓ phosphorylase & ↓ gluconeogenesis.

2- ***Lipid***: ↑ Lipogenesis by ↑ Lipoprotein lipase & ↓ Lipolysis by ↓ Triglyceride lipase → ↓ Circulating free fatty acids (FFA).

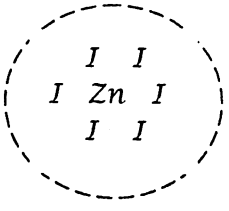
3- ***↓ Ketone body formation*** e.g. Acetone, Acetoacetic & β-Hydroxybuteric acids.

4- ***Proteins***: Anabolic → ↑ Amino-acid uptake by Sk.m. → Protein. ↓ Catabolism → +ve Nitrogen balance.

5- ***Gene*** expression → Nucleoprotein synthesis.

6- ↑ Cellular uptake of ***K^+, Ca^{+2} & phosphate*** → ↓ Their plasma levels.

*Preparations of Insulin:



A) Natural Unmodified Insulin = Soluble Insulin:

1-***Regular*** = Crystalline Zinc Insulin → Either acidic or neutral.
2-Water soluble → Fast acting & can be injected SC, ***IM & IV in emergencies***. الوحيد
3-Kinetics: ***Onset*** (1/4-1/2 hour), ***Peak*** (2-4 hours) & ***Duration*** (5-8 hours)
4-Disadvantages:
- a-Short Duration → Multiple injections/day.
- b-Acidic insulin → Irritant → subcutaneous atrophy or hypertrophy (lipodystrophy).

B) Modified Insulins:

1- Ultrashort Acting:

a-***Insulin Lispro***.
b-Insulin analogue synthesized by recombinant DNA (Lysin ↔ Prolin in chain B).
c-It is monomer → Rapid absorption after SC injection, while regular insulin is hexamer.
d-Kinetics: ***Onset*** (1/4-1/2 hour), ***Peak*** (1 hour), ***Duration*** (3-4 hours).

2-Short Acting Insulins:

a-***Semilente Insulin*** = Prompt or Amorphous Insulin Zinc Suspension.
b-Kinetics: ***Onset*** (1/2-1 hour), ***Peak*** (4-6 hours), ***Duration*** (12-16 hours).

3-Intermediate Acting Insulins:

a-Kinetics: ***Onset*** (1-2 hours), ***Peak*** (6-12 hours), ***Duration*** (18-24 hours)
b-***Lente Insulin*** = Insulin Zinc Suspension = 30% Semilente + 70% Ultralente
c-***Isophane Insulin = Neutral Protamine Hagedorn (NPH) Insulin***: Contains balanced amounts of Insulin, Zn & protamine → does not precipitate soluble insulin → Can be mixed
d-***Insulin Glargine***: Insulin analogue (Glycine + Arginine) → Sustained *peakless* absorption. Acidic pH = 4 → Not mixed with other insulins ***Onset*** (2-5 hours), ***Duration*** (18-24 hrs).

4-Long Acting Insulins:

a-Kinetics: ***Onset*** (4-6 hours), ***Peak*** (16-20 hours), ***Duration*** (20-36 hours).
b-***Ultralente Insulin*** = Extended or Crystalline Insulin Zinc Suspension.
c-***Protamine Zinc Insulin suspension (PZI)***: Highly alkaline & contains excess protamine & zinc → precipitate soluble insulin → NOT mixed together in the same syringe.

	Onset	Peak	Duration	Remarks
A) Ultrashort Acting:				
1- Insulin Lispro	1/4 - 1/2 hr	1 hour	3-4 hours	Monomer
B) Short Acting:				
1- Soluble (Regular) :	1/4-1/2 hr	2 - 4 hours	5 - 8 hours	ONLY one IV
2- Semilente	1/2 – 1 hour	4 – 6 hours	12 – 16 hours	Amorphous
C) Intermediate Acting:				
1- Lente :	1-2 hr	6-12 hr	18-24 hr	30% S + 70% U
2- Isophane (NPH) :	1-2 hr	6-12 hr	18-24 hr	+ Soluble
3- Insulin glargin	2-5	5 → 24	18-24	Peakless
D) Long Acting:				
1- Ultralente :	4-6 hr	16-20 hr	20-36 hr	Crystalline
2- Protamine Zinc :	4-6 hr	16-20 hr	20-36 hr	NOT + Soluble

*Source of Insulin:

1-**Animal**:
  a- Bovine: 3 Amino-acids difference from human → Antigenic.
  b- Porcine: 1 Amino-acid difference form human → Less antigenic.
2-**Humanized Insulin**: Modification of animal insulin → Human insulin.
3-**Recombinant Insulin**:
  a- Human.
  b- Analogues e.g. Lispro & Glargine.
4- One mg of Insulin = 22 U.

NB) Diabetes Mellitus (DM)

DM is metabolic disorder due to Absolute or Relative insulin deficiency.

* Characterized by :

1- ↑ Glycogenolysis, Gluconeogenesis & ↓ Uptake of glucose by tissues → Hyperglycemia → Glucoseuria → Polyuria → Polydepsia.
2- Polyphagia BUT loss of weight.
3- ↑ Lipolysis & ↓ Lipogenesis → Hyperlipidemia → Ketonemia (Ketosis) → Ketonuria.
4- ↑ Catabolism → Azotemia → Azoturia
5- Weakness, ↓ Immunity & Recurrent infections.

* Classification of DM :

A) Primary DM:

1- Type I (Juvenile-Onset DM, Age of onset < 30 Years) :

a- Due to ABSOLUTE insulin deficiency = True hypoinsulinism.
b- ALL are Insulin Dependent Diabetics (IDD).
c- Mostly NON-Obese.

2- Type II (Adult or Maturity-Onset DM, Age of onset > 40 Years) :

a- Usually due to RELATIVE insulin deficiency = Relative hypoinsulinism.
b- Usually, they are Non-Insulin Dependent Diabetics (NIDD).
c- Usually OBESE (85% of patients). Obesity → Down-regulation of insulin Receptors. Over-eating → Excess Insulin Release → Excess internalization of receptors → ↓ Available receptors → Down regulation. The number of available receptors are inversely proportion to serum insulin

	Type I	Type II
1- Age of Onset :	Usually < 30 years	Usually > 40 years
2- Insulin deficiency :	True (Absolute)	Relative
3- Treatment with Insulin:	Always necessary → IDD	Usually NOT necessary → NIDD
4- Body weight :	Non-Obese	Usually Obese (85%)
5- Ketosis :	Marked	Absent.
6- Islet cell antibodies :	Yes	No
7- HLA association :	Yes	No

* HLA = Human Leukocyte Antigen

B) Secondary DM:

1- Alloxan & Streptozotocin: Selective cytotoxic effect on β-Cells.
2- Immuno-suppressives: They inhibit insulin synthesis.
3- Inhibitors of Insulin Release: α_2-Agonists, β_2-Antagonists, Thiazide diuretics, Diazoxide & Phenytoin.
4- Counter-regulating hormones e.g. Glucagon, Glucocorticoids, Growth hormone, Thyroid, Oral contraceptives & Catecholamines.

* *Indications of Insulin:*

A) Diabetes Mellitus:

- **Insulin is essential & a true replacement therapy in patients with I.D.D.**
- **Insulin is *NOT* essential (But NOT Contraindicated) in patients with N.I.D.D.**

1- ALL cases of Insulin Dependent Diabetes Mellitus (IDDM):
   a- All cases of Type-I diabetics.
   b- Some cases of Types-II diabetics after failure of Diet regulation + Exercise + Oral hypoglycemics.
2- Temporary in N.I.D.D. during STRESS periods e.g. Infection, Operation & Pregnancy.
3- Permanently in N.I.D.D. with renal impairment.
4- Emergency treatment of Diabetic Ketoacidosis & Non-ketotic Hyperosmolar Diabetic coma.

B) Other Indications:

1- Hyperkalemia due to renal failure.
2- Anorexia nervosa.
3- Test after gastrectomy.
4- Mental disorders.

A) Routes of Administration of Insulin:

1- Parenteral: All → S.C.. Soluble insulin can be injected I.M. & S.C. in emergencies.
2- Nasal Spray & Inhalation (Under trials)

B) Methods of Parenteral Administration:

1- Disposable plastic syringes.
2- Pen injection device.
3- Insulin pump ± Glucose sensor.

C) Regimens of Insulin Therapy:

1- ***Single*** daily injection of Intermediate Acting ± Soluble (70% + 30%) insulins in single dose 30 minutes before breakfast.
2- ***Twice*** daily injections of Intermediate acting + Soluble insulin before breakfast (2/3 daily dose) & before supper (1/3 daily dose). Most common.
3- ***Multiple*** daily injections of Intermediate + Soluble insulins
   a- Intermediate acting insulin before breakfast ± Supper.
   b- Soluble insulin 30 minutes before the 3 main meals.

D) Assessment of Diabetic Control (Patient Compliance):

1- Urine analysis for glucose ± Ketone by using test strips.
2- Blood sugar monitoring (Home or Laboratory).
3- Glycosylated hemoglobin (HbA_1) & serum fructosamine → Long term control.

E) Factors that (↑) Increase Insulin Requirements:

1- Infection, Operation, Pregnancy & Trauma.
2- Treatment with counter-regulating hormones or drugs.
3- Severe liver dysfunction. Normally the liver secretes Insulinase-inhibitor.
4- Specific antagonists e.g. High insulinase activity & insulin antibody formation.

F) Factors that (↓) Decrease Insulin Requirements:

1- Physical exercise → ↑ Glucose uptake & utilization by tissues.
   Daily insulin requirements are inversely proportional to degree of physical activity.
2- A decrease in caloric intake. Diet regulation & weight reduction resumes sensitivity to insulin and oral hypoglycemics.

* Adverse Effects of Insulin:

A) Local Reactions:

1- Hypersensitivity reaction e.g. Redness & itching → Usually subside spontaneously.
2- Secondary infection (Very rare).
3- Subcutaneous Lipodystrophy → Lipo-hypertrophy or Lipo-atrophy.
Can be avoided by frequent change site of injection.

B) Systemic Reactions:

1- Hypersensitivity (Allergic) reaction → Generalized rash, urticaria, angio-edema & anaphylactoid reactions:
   a- Change protamine-containing insulin to an equivalent non-protamine insulin e.g. N.P.H. (Isophane) → Lente Insulin , P.Z.I. → Ultralente Insulin.
   b- Change animal species & BETTER use human insulin
   c- Immuno-therapy may be required.

2- Insulin resistance due to high activity of insulinae enzyme or over production of Insulin antibodies.

3- Hypoglycemia:

*Causes:

1- Too much or bad timing of insulin → True Hyper-insulinism.
2- Too little food intake or missing meal. } Relative Hyper-insulinism
3- Too much muscular exercise.

*Manifestations:

1- Sympathetic → Sweating, pallor, tachycardia & tremors.
2- Neuro-glyco-penia → Hunger, headache, irritability, weakness, blurring of vision, confusion, convulsions & coma. If prolonged → Permanent brain damage & Death.
3- Laboratory → Low blood sugar & Urine is –ve for glucose.

*Treatment:

1- If patient is conscious → Oral glucose or sweets.
2- If patient in Coma = Unconscious →
   a- I.V. Glucose 50 ml 50% → Life saving.
   Then flush the vein with saline to avoid thrombosis & sclerosis.
   b- Glucagone 1 mg S.C. or I.M. if sterile glucose is not available.
   c- Adrenaline 1 mg S.C. if No alternative & No C.V.S. contraindications.

4- Somogyi Effect → Rebound morning hyperglycemia (due to excess release of counter-regulating hormones) that follows insulin-induced hypoglycemia during night. Avoided by reducing the evening dose of insulin.

5- Weight gain.

Treatment of Complications of Diabetes Mellitus

*Diabetic Coma (Keto-acidosis):

A) Causes:

1- Too little insulin = Bad patient compliance.
2- Too much food intake.
3- Stress e.g. Infection, Operation, Pregnancy, trauma & emotional stress.

B) Manifestations:

1- Stupor & coma.
2- Acetone smell in breath.
3- Polydepsia, polyuria & dehydration.
4- Tachycardia.
5- Anorexia, nausea, vomiting & abdominal pain.
6- Laboratory → Blood (Hyperglycemia & acidosis) & urine (Glucosuria & acetone)

C) Treatment:

1- For Hyperglycemia:

- Soluble (Regular) Insulin: 0.1 U / kg I.V. injection + 0.1 U / Kg / Hour I.V. infusion or I.M. till glucose in blood drops to < 300 mg%.

2- For Dehydration & Electrolytes:

a- Saline I.V. (0.9 % NaCl) Infusion till glucose in blood drops to < 300 mg% → Then
b- Glucose 5% I.V. Infusion to avoid hypoglycemia.
One g Glucose = 20 ml of Glucose 5% for each 1 U Insulin.
c- KCl or K-Alkaline-Phosphate to avoid hypokalemia.
Better taken orally after recovery. Monitor E.C.G.

3- For Acidosis & Ketosis if pH of Blood < 6.9 :

a- Na lactate 1.85% I.V. infusion (One volume Na lactate for each 2 volumes Saline).
b- Ringer lactate I.V. infusion.
c- $NaHCO_3$ I.V. infusion.

4- For Infection:

a- Naso-gastric aspiration.
b- Aspiration of respiratory secretions.
c- Antibiotics.

5- After Recovery:

a- Treat underlying cause.
b- Diabetic ketoacidosis occurs ONLY to Type-1 I.D.D. → Resume Insulin therapy.

*Non-Ketotic Hyperosolar Diabetic Coma:

1- Occurs in N.I.D.D. with bad compliance.
2- Severe Hyperglycemia → Polyuria → Dehydration → ↑ Osmolarity of blood.
3- No ketosis.
4- Same lines of treatment for Diabetic keto-acidosis But no need to alkalis.
5- After recovery → Resume Oral anti-diabetic therapy.

Oral Anti-Diabetic Drugs

I- Insulin Secretagogues = Oral Hypoglycemic Drugs

A) Sulfonylurea Group

*Preparations:

A) First Generation:

1- Short acting (6-12 hours) → **Tobutamide** (*Diamol*, 1/2-1 g bid or tds).
2- Intermediate acting (12-24 hours) → **Acetohexamide** (1/4-1.5 g od or bid).
3- Long acting (up to 60 hours) → **Chlorpropamide** (*Pamidine*, 0.1-0.5 g od)
Chlorpropamide → Potentiate ADH on Nephron → Anti-diuretic effect.

B) Second Generation:

- More potent & Less side effects
- Intermediate acting → up to 24 hours

1- **Glibenclamide** (*Daonil*) → 2.5 – 20 mg od or bid.
2- **Glipizide** (*Minidiab*) → 2.5 – 15 mg od or bid
3- **Gliclazide** (*Diamicrone*) → 40 – 160 mg od or bid
4- **Glimepiride** (Amaryl) → 1 - 3 mg od ± Insulin.

*Kinetics:

1- Absorbed orally.
2- Distributed all over the body and pass BBB & placental barrier
3- Metabolized in liver. *Acetohexamide → Active metabolite.*
4- Excreted in urine

*Mechanism of Action:

1- They depend on the presence of endogenous insulin (about 30% functioning β-cells):
   a- They **Block** ATP-sensitive K^+-channel (K_{ATP}-Channels) of β-Cells of Pancreas → Depolarization → Influx of Ca^{2+} → Excocytosis → ↑ **Release of Insulin**.
   b- Sensitize β-Cells to effect of Glucose → ↑ **Release of Insulin.**
   c- Inhibit release of catecholamines (Anti-insulins) → ↑ **Release of Insulin.**
2- ↓ release of Glucagon (Directly or through ↑ Insulin & Somatostatin).
3- Extra-pancreatic effect → ↑ No. & sensitivity of insulin receptors → Potentiate peripheral actions of Insulin e.g. Anti-lipolytic & Anti-glycogenolytic effects.

*Indications of Sulfonylureas:

1- Non-Insulin Dependent Type-II Diabetes (NIDD) after failure of Diet regulation & exercise. They are more effective in mild diabetics with daily requirements of insulin < 30 U / day.
   a- Non-Obese (Sulphonylureas ↑ Appetite).
   b- Non-Complicated Diabetes:
      - No stress e.g. Infection, Operation or Pregnancy.
      - No Major organ disease e.g. Cardiac, hepatic or renal.
      - No History of diabetic ketoacidosis.
2- Chlorpropamide → Anti-diuretic → Treat Hypothalamo-pituitary Diabetes insipidus.

*Contraindications of Sulfonylureas:

1- Type-I Insulin Dependent Diabetes (I.D.D.).
2- N.I.D.D. during stress periods e.g. Infection, operation & trauma.
3- Pregnancy & Lactation: Sulphonylureas pass placental barrier → Teratogenic & hypoglycemia of neonate.
4- History of diabetic ketoacidosis.
5- Severe hepatic or renal diseases.

*Adverse Effects of Sulfonylureas:

1- Hypoglycemia especially → Overdose, Elderly or Liver or kidney diseases.
2- ↑ Appetite → Weight gain.
3- **A**llergy = Hypersensitivity & cross-allergy with other sulfonamides e.g. Thiazides.
4- **B**one marrow inhibition.
5- **C**holestatic jaundice.
6- **D**isulfiram-like action → Alcohol intolerance.
7- **E**dema due to its anti-diuretic effect.

} Especially Chlorpropamide.

8- **F**ailure:
   a- Primary failure in 10 - 15 % of N.I.D.D.
   b- Secondary failure after long use (years) due to exhaustion β-Cells.
9- **G**.I.T. disturbances → Heart burn, nausea, vomiting & diarrhea.
10- ↑ Incidence of coronary **H**eart disease.
11- C.N.S. manifestations → Headache, confusion, vertigo & ataxia.
12- Teratogenic.

*Drug Interactions of Sulfonylureas:

1- Aspirin, Phenylbutazone & sulfa → Displace sulfonylureas → Hypoglycemia.
2- Sulphonylureas → Displace Oral anticoagulants → Bleeding.
   Dicoumarol → ↓ Excretion of Chlorpropamide.
3- Phenobarbitone, Phenytoin & Rifampicin → ↑ HME → ↑ Metabolism of Sulphonylureas.
4- MAO-I, Allopurinol, Cimetidine & Chloramphenicol → ↓ Metabolism of Sulphonylureas.
5- β-Blockers e.g. Propranolol:
   a- Augment their hypoglycemia & ↓ compensatory hepatic glycogenolysis.
   b- Mask sympathetic manifestation of hypoglycemia → Silent coma.
6- Thiazides, Corticosteroids & Contraceptives decrease the action of sulphonylureas.

B) Other Insulin Secretagogues

1- **Examples**:
   a- **Meglitinides** e.g. ***Repaglinide*** *(Novonorm, ½ - 2 mg before each meal).*
   b- **D-Phenylalanines** e.g. ***Nateglinide*** *(Starlix, 120 mg before each meal).*
2- No cross-allergy with Sulphonylurea.
3- Pharmacodynamics → Similar to Sulfonylureas.
4- Rapid onset of action (Peak = 1 hour) & Short t1/2 = 2-3 hours.
5- Given before each meal → Control post-prandial hyperglycemia & HbA_{1C}.
6- Better used with Metformin *(Starlix combi = Nateglinide + Metformin)*
7- Adverse effects → Hypoglycemia & weight gain.

II- Insulin Sensitizers = Euglycemics

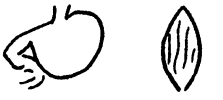
A) Biguanides

*Preparations:

1- **Metformin** *(Glucophage)* ½ g tds with meals
2- **Phenformin** → Obsolete.

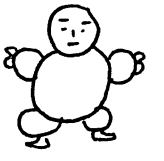
*Mechanism of Action:

1- They do ***NOT*** stimulate the release of insulin → No hypoglycemia ***BUT*** euglycemia.
2- Decrease glucose absorption from the intestine.
3- Increase glucose uptake by skeletal muscle.
4- Decrease hepatic gluconeogenesis.
5- Increase anaerobic glycolysis in peripheral tissues → ↑ Removal of glucose from the blood → ***BUT*** ↑ Lactic acid production.
6- Decrease release of Glucagon.
7- Increase sensitivity of tissues to insulin by ↑ binding to its receptors.



*Therapeutic Uses of Metformin:

1- Obese (Biguanides ↓ Appetite) Non-Insulin Dependent Diabetes (N.I.D.D.) after failure of diet regulation & exercise.
2- Can be combined with Sulphonylureas & Insulin.



*Adverse Effects of Biguanides;

1- G.I.T. → ***Anorexia***, nausea, vomiting & diarrhea.
2- ***Lactic Acidosis*** especially Phenformin in patients with:
   a- Hepato-cellular failure → Can not metabolize lactic acid.
   b- Renal insufficiency → Can not excrete lactic acid.
   c- Hypoxic states e.g. Cardiac & pulmonary diseases.
   d- Advanced age & chronic alcoholism.
3- Long use of Metformin ↓ absorption of Vitamin B-12.

	Sulphonylureas	*Biguanides*
1- Example	Glibencalmide	Metformin
2- Mechanism	↑ β-Cells → ↑ Release of Insulin	Not ↑ Release of Insulin
3- Effect	Hypoglycemia	Euglycemic
4- Appetite & Weight	↑	↓
5- Use	Non-Obese N.I.D.D.	Obese N.I.D.D.
6- Adverse effects	Hypoglycemia, ↑ Appetite + ABCDEFGH	Lactic acidosis

B) Thiazolidinediones (Glitazones):

1-Examples:
- a- **Rosiglitazone** *(Avandia, 4 mg od po)*
- b- **Pioglitazone** *(Glustin, 15 – 30 mg od po)*

2- *Mechanism*: They bind to specific nuclear receptor (Peroxisome-Prolifrator-Activator-Receptor-Gamma = PPAR-γ) → In insulin-sensitive tissues e.g. adipose, sk.m. & liver → Gene expression → Synthesis of cellular molecules important for insulin signaling e.g. Lipoprotein lipase enzyme & Glut-4. Their effect appears within 1-2 months.

3- *Useful* as monotherapy or with Sulphonylureas or Metformin in N.I.D.D.

4-Adverse Effects of Glitazones:
- a- Troglitazone → Hepatotoxic → Obsolete.
- b- Anemia. c- Fluid retention
- d- Hepatic microsomal enzyme induction → ↑ Metabolism of contraceptives.
- e- Induction of ovulation in some anovulatory females → Unexpected pregnancy.

* *Other Oral Anti-Diabetic Drugs:*

Alpha-Glucosidase Inhibitors:

1-Examples:
- a- **Acarbose** *(Glucobay) 50 – 100 mg tds po with the first mouthful.*
- *b-* **Miglitol**.

2- ↓ α-Glucosidase on brush border of intestinal mucosa → ↓ Absorption of complex Carbohydrates→ ↓ Postprandial hyperglycemia.

3- Useful in Type-II N.I.D.D. either alone or with Sulfonylurea but **Not** Metformin.

3-Adverse Effects : Flatulence, diarrhea & ↓ absorption of Metformin.

Management of Diabetes Mellitus

*Management of Type I DM "< 30 years" (IDDM) :

Insulin + Diet + Exercise

**Management of Type II DM "> 40 years" (NADDM) :*

I- Start with **(Diet Regulation + Exercise).**

II- If the above **(Diet Regulation + Exercise)** FAIL to control DM →

A) If Obese:

1- Monotherapy → **Metformin** (or Acarbose) → If failed →
2- Add a sulfonylurea → If Failed →
3- Add a glitazone → If failed
4- Stop the Sulfonylurea (Continue Metformin & Glitazone) & Start Insulin therapy.

B) If Non-Obese:

1- Monotherapy → **A Sulphonylurea** → If failed →
2- Add Metformin → If failed →
3- Add Glitazone → If failed
4- Stop the Sulfonylurea (Continue Metform & Glitazone) & Start Insulin therapy.

III- If STRESS (Infection, Operation & Pregnancy), STOP TEMPORARLY Oral hypoglycemics and USE Soluble Insulin S.C. 30 minutes before the 3 main meals till recovery then GO BACK to the PREVIOUS treatment.

IV- If RENAL IMPAIREMENT, STOP PERMANENTLY Oral hypoglycemics & use Intermediate Acting Insulin e.g. Lente or Isophane (NPH) Insulin forever.

*Management of Diabetic Complications

1- Hypoglycemia (see page 21)
2- Diabetic ketoacidosis (See page 22)
3- Non-ketotic Hyperosmolar coma (See page 22)

Anti-Diabetic Measures

I- Diet Regulation: Important to all diabetic patients.

A) *Total Caloric Intake*:

1- Depends on Age, Physical activity & Deviation form ideal weight:
   a- Average weight (30 c/kg) b- Underweight (40 C/kg) c-Overweight (20 C/kg).
2- Weight reduction by caloric restriction in obese type II diabetics → Restore sensitivity to circulating Insulin.
3- Type I diabetics are seldom obese. Adequate diet is essential for growing children.

B) *Dietary Composition*:

1- Carbohydrates: 50-60% of total caloric intake, mainly complex CHO (Starchy food e.g. polysaccharides)
2- Proteins: 15-20% of total caloric intake.
3- Fat < 30% of total caloric intake (Plant oil is BETTER than Animal fat) :
   a- ↑ Unsaturated fat e.g. Olive oil & Palm oil.
   b- ↓ Saturated fat e.g. Butter & Ghee.
   c- Cholesterol intake < 300 mg/day.
4-↑ Dietary fibers e.g. Bran, green vegetable & fruits → ↓ Absorption of glucose & cholesterol.

C) *Timing & Size of Meals*:

1- Breakfast should be eaten within 1/2 hour after the morning insulin dose.
2- 3 Main meals + 3 Snacks in between and at bed time.

D) *Sweeteners*: Aspartame (NutraSweet), 2 amino-acids (Aspartic acid and Phenylalanine),180 times > sucrose BUT heat labile.

E) *Vitamins:* Specially Vit B-1 & B-12

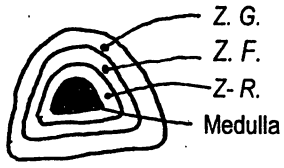
II- Exercise: ↑ Glucose uptake & utilization by tissues.

III- Drugs: Insulin and Oral Antidiabetics.

Adrenocortical Hormones (Corticosteroids)

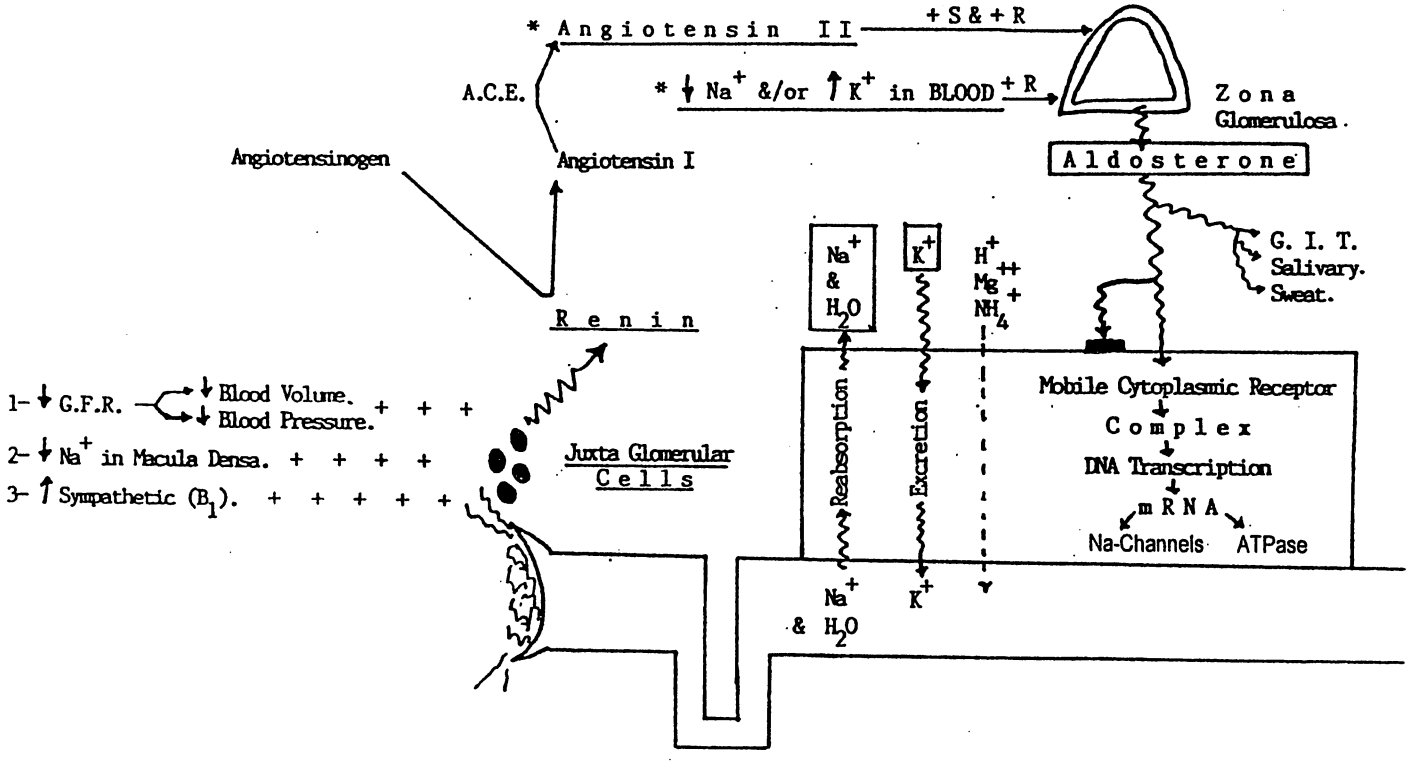
Steroid hormones secreted from adrenal (suprarenal) cortex → Essential for life

1- Zona glomerulosa → Mineralocorticoids e.g. Aldosterone & D.O.C.
2- Zona fasciculata & Zona reticularis:
   a- Glucocorticoids e.g. Hydrocortisone (Cortisol).
   b- Sex hormones e.g. Androgen & Estrogen.



1- Aldosterone

- Steroid hormone synthesized and secreted from Zona glomerulosa.
- Very powerful mineralocorticoid & very weak glucocorticoid activity.



*Control Of Release of Aldosterone:

A) Renin-Angiotensin System (RAS):

1- Renin enzyme is secreted from Juxta-Glomerular Cells (JGC) in response to:
   a- ↓ G.F.R.: ↓ Blood volume & / or ↓ Blood pressure.
   b- ↓ Na^+ in Macula densa.
   c- ↑ Sympathetic tone → ↑ β_1-adrenoceptors in the kidney.
2- Renin converts Angiotensinogen → Inactive Angiotensin-I.
3- A.C.E. converts Inactive Angiotensin-I → Active Angiotensin-II → ↑ AT-1 receptors → ↑ BOTH synthesis and release of Aldosterone.

B) ↓ Na^+ &/or ↑ K^+ in blood → ↑ Zona glomerulosa directly → ↑ Release of Aldosterone.

*Dynamics of Aldosterone:

A) Kidney:

1- **Effect**: Sodium & Water Retention + Depletion of K^+ (Mainly), H^+, Mg^{2+} & NH_4^+.
2- **Result**: ↑ Na^+, ↑ H_2O & ↓ K^+ in Blood → ↑ Blood volume & pressure → ↑ RBF, ↑ GFR → ↓ Renin.
3- **Site of Action** → Distal Convoluted Tubules of the nephron.
4- **Mechanism Of Action Of Aldosterone**:
   a- *Genomic effect* → Most of actions. Aldosterone being steroid → Lipid soluble → Gain access intra-cellularly by passive diffusion → Bind to cytoplasmic receptor → Activation → ↑ Nuclear receptors → Gene expression → DNA transcription → mRNA → Protein synthesis → Na^+-channels & Na^+/K^+ ATPase.
   b- *Non-Genomic effect*: Aldosterone → ↑ Membrane receptors → ↑ Na^+/K^+ Exchange.
5- **The effect** of Aldosterone:
   a- Potentiated by Glucocorticoids (Cortisol).
   b- Antagonized by Progesterone & Spironolactone.
6- **Escape Phenomenon**: Prolonged hypervolemia → ↓ Sensitivity of D.C.T. to the effect of Aldosterone → NO Na^+ & Water retention *BUT* still K^+ excretion.

B) G.I.T., Salivary & Sweat Glands:

- Similar to D.C.T. *BUT* Weaker, delayed & NO escape phenomenon.

*Causes of Hyper-Aldosteronism:

1- Primary → Adenoma in Zona glomerulosa → Conn's disease.
2- Secondary to Heart failure, Nephrotic syndrome & Liver disease e.g. Cirrhosis.

*Therapeutic Uses of Aldosterone:

Aldosterone is rarely used clinically. But its antagonist (Spironolactone) is useful as K^+-Retaining diuretic especially in cases of Hyper-aldosteronism.

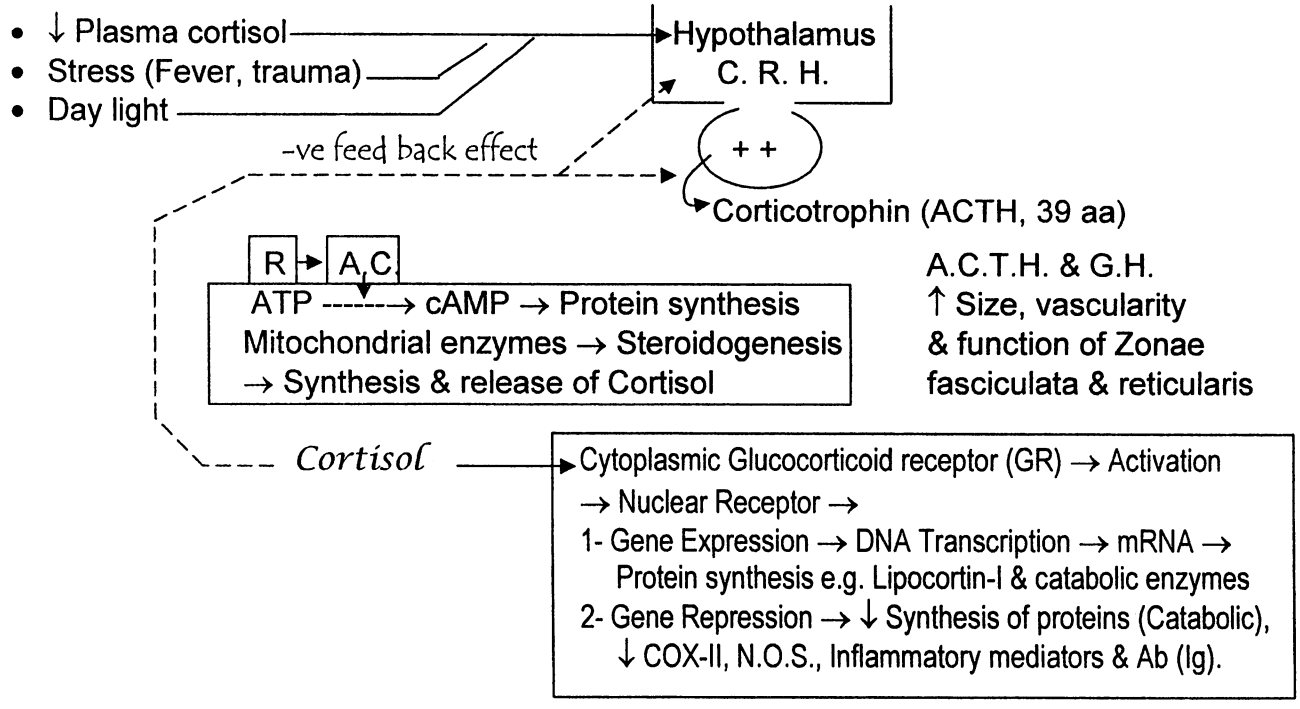
2- *Des-Oxy-Corticosterone (D.O.C.)*

1- ***Pure*** mineralocorticoid with ***NO*** glucocorticoids activity.
2- 1/100 activity of aldosterone.
3- Used to replace mineralocorticoid activity in Addison's disease.
4- NOT effective orally due to extensive hepatic first pass metabolism.
5- Preparations:
   a- Desoxycorticosterone Acetate (D.O.C.A.):
      - Sublingual: 2 – 6 mg / day.
      - I.M.: 1 – 3 mg / day.
      - Subcutaneous Pellet Implantation: 75 mg / 6 months.
   b- Desoxycorticosterone Trimethyl Acetate: 25 – 100 mg I.M. / month

3- *Fludrocortisone Acetate* (9-α Fluoro-Hydrocortisone)

1- Synthetic mineralocorticoid.
2- Mineralocorticoid (125 X Cortisol) & Glucocorticoid (10 X Cortisol) activities.
3- Useful orally (0.1 – 0.3 mg) to replace mineralocorticoid activity in Addison's disease.

Hydrocortisone (Cortisol)



*Adreno-Cortico-Trophic-Hormone (A.C.T.H.):

Polypeptide hormone (39 amino acids) secreted by basophil-cells of anterior pituitary.

A) Control Of Release Of A.C.T.H.:

1- ↓ Plasma cortisol → ↑ Hypothalamus → ↑ Corticotrophine Releasing Hormone (C.R.H.) → ↑ Anterior Pituitary → ↑ A.C.T.H.
2- Stress eg Infection & Trauma → ↑ BOTH Hypothalamus & Anterior pituitary → ↑ ACTH.
3- Others:
   a- Adrenaline, A.D.H. & Estrogen → ↑ A.C.T.H.
   b- Androgen & Opiopeptides → ↓ A.C.T.H.
4- Day light → ↑ A.C.T.H.; while at night → ↓ A.C.T.H. = Circadian rhythm.

B) Mechanism Of Action Of A.C.T.H.:

1- A.C.T.H. (Polypeptide) → Binds to membrane receptor in Zonae fasciculata & reticularis → ↑ Adenylate cyclase → ↑ cAMP → Protein synthesis → Mitochondrial enzymes essential for steroidogenesis → Synthesis & secretion of Cortisol.
2- A.C.T.H. & to lesser extent G.H. → ↑ Size, vascularity & function of Zonae fasciculata & reticularis
3- A.C.T.H. has almost *NO* effect on Zona glomerulosa → *NO* effect on Aldosterone.

C) Therapeutic Uses of A.C.T.H.:

1- Preparations:

a- Corticotrophin (A.C.T.H.)
b- Synthetic Tetracosactrin "*Synacthen*" → First 24 amino acids of A.C.T.H. → Same effect of A.C.T.H. & less antigenic.

2- Indications → ↑ Synthesis & Release of Cortisol

a- Same indications of Cortisol (*Except* primary Addison's disease) especially in children & elderly.
b- Help withdrawal of steroid therapy after long use.
c- Test the function of adrenal cortex → Estimate plasma cortisol.

Actions	Side Effects	Contraindication	Precautions	Therapeutic Uses
1- **M** etabolic a→ CHO → Gluconeogenesis	Iatrogenic Cushing's disease	Cushing's disease		Addison's disease
→ Glycogenesis (Liver)				
→ ↓ Glucose uptake	Hyperglycemia	Diabetes mellitus	Sugar in urine	
b→ Fat → Lipolysis				
→ Lipemia				
→ Redistribution	Moon face & Buffalo hump		X-ray spine	
c→ Protein → Most tissues → Catabolic	Osteoporosis	Osteoporosis	↑ protein in diet Anabolics	
2- **E** lectrolytes → Minerla- a→ Na^+ & water retention	Edema & Hypertension	Heart failure & Hypertension	Weight , Bl.p.	
b→ K^+ depletion		Digitalis toxicity	Digitalis toxicity	
NB) ↑ Free water clearance (glucocorticoids)			↓ NaCl & ↑ K^+	
3- Anti-**In** flammatory & Anti-Rheumatic	Mask infections	Untreated infections		Inflammations
4- **G** astric → ↑ HCl & ↓ mucin	Peptic ulcer	Peptic ulcer		
5- ↓ **A** ntibody formation & ↓ Antigen/Antibody reaction	↓ Immunity & ↑ Infection	Viral infections		Allergy Auto-immune
6- **B** lood a→ ↑ RBCs & ↑ PMNL				Tissue graft
b→ ↑ Platelets				
c→ ↑ Coagulation	Thrombosis	Thrombo-embolism		
d→ ↓ Lymphocytes				Lymphoma & leukemia
e→ ↓ Eosinophils				
7- **EU** phoria	Psychological disturbances	Psycho. Disturbances		
8- ↓ **P** ituitary A.C.T.H.	Sudden stop → Addison's Crisis	Sudden withdrawal	Gradual withdrawal	Adreno-genital syndrome
9- **W** ound healing	Delay wound healing			Keloid formation
10- **U** ricosuric				Gout
11- Anti – **S** hock & Anti- Stress			↑ dose in stress	Shock
12- Anti – **V** itamin D	Hypocalcemia		↑ Ca^{2+}	Hypervitaminosis D (Hypercalcemia)
	Sublaxation of joints	Repeated intra-articular		
	Myopathy			
	Retard growth in children			
	Teratogenic	Pregnancy		
	Cataract & Glaucoma	Glaucoma		

*Mechanism Of Action Of Cortisol:

1- **Genomic Mechanism**: Cortisol → Steroid → Lipid soluble → Gain access intracellularly by passive diffusion → Bind to cytoplasmic glucocorticoids receptor (GR-α & GR-β) → Activation → Nuclear receptors:
   a- **Gene expression** → DNA transcription → mRNA → Protein synthesis e.g. Lipocortin-I (Annexin-1) & catabolic enzymes.
   b- **Gene repression** → ↓ Protein synthesis (Catabolic) → ↓ COX-II, Nitric oxide Synthase, Inflammatory mediators & Immunoglobulins (Antibodies).
2- **Non-genomic Mechanism**: Cortisol ↑ membrane receptors e.g. in Hippocampus.

*Pharmacological Actions Of Cortisol:

All actions are considered as Glucocorticoid activity *except* on Na^+ & K^+ (mineralo-).

1- Negative Feed back effect on A.C.T.H.:

a- ↓ Release of C.R.H. from hypothalamus.
b- ↓ Release of A.C.T.H. from Anterior pituitary.

2- Organic Metabolism:

A) Carbohydrates (CHO):

1- Gluconeogenesis: Cortisol mobilizes amino-acids from Sk.m. proteins → Uptake by liver → Convert them into CHO & urea.
2- ↑ Glycogenesis by liver: ↑ The conversion of pyrovate to glycogen & ↓ release of glucose from the liver.
3- Anti-Insulin effect → ↓ Glucose uptake & utilization by peripheral tissues → Hyperglycemia.

B) Proteins → Catabolic effect:

1- Catabolic effect & -ve Nitrogen balance: ↑ Conversion of amino-acids into urea → ↑ Urea excretion in urine.
2- Catabolic effect on Lymphatic tissue, connective tissue, fibroblast, skeletal & bone (↑ Osteoclst & ↓ Osteoblast activities) → Osteoporosis.

C) Fat:

1- Lipolysis → ↑ Free Fatty Acids in blood → Lipemia.
2- Redistribution of fat depot → Deposition of fat in facio-cervico-trunkal region → Moon face & Buffalo hump.

3- Electrolytes → The ONLY mineralocorticoid activity:

a- $Na^+ + H_2O$ retention & K^+ depletion → Hypernatremia + Hypervolemia + Hypokalemia
b- Hypervolemia → ↑ RBF → ↑ GFR → ↑ Na^+ Excretion → # Partially Na^+ retention.

4- Free Water Clearance: Glucocorticoid activity

a- Cortisol ↓ Permeability of D.C.T. to free water → Maintain the ability of kidney to excrete a water load.
b- In Addison's disease → No diuretic response to water load → Water intoxication.

5- C. V. S.:

a- Na^+ & Water retention → Hypervolemia → ↑ C.O.P. } **Hypertension**
b- Potentiate V.C. of Noradrenaline & Angiotensin → ↑ T.P.R. }
c- ↓ Capillary permeability.

6- Anti-inflammatory & Anti-Rheumatic Effect:

a- *Non-specific* anti-inflammatory irrespective of the cause whether physical, chemical, infection or immune.

b- Treats the manifestations rather than the cause → *Deceiver*.

c- **Mechanism**:

- Synthesis of a **Lipocortin-1 = Annexin-1** (polypeptides, *Lipomodulin by Neutrophils + Macrocortin by Macrophages)* → ↓ ***Phospholipase A_2 enzyme*** → ↓ Arachidonic acid → ↓ PGs, LTs & P.A.F.
- **Repress** genes of COX-II, inducible NOS, adhesion molecules & complement components.
- ↓ Formation of other inflammatory mediators & cytokines e.g. ILs, TNFα & CSF.
- ↓ Migration of leukocytes to site of inflammation.
- Stabilization of lysosomal membrane → ↓ Cell death.
- ↓ Capillary permeability → ↓ Inflammatory edema & joint effusion.

7- Stomach: ↑ HCl & ↓ Mucin secretion → Worsens Peptic ulcer.

8- Anti-Allergic & Immunosuppressant:

a- ↓ Antibody formation.

b- ↓ Antigen / Antibody reaction.

c- Stabilization of mast cell → ↓ Degratulation → ↓ Release of allergic mediators.

d- ↓ Tissue response to allergic mediators.

9- Blood:

a- ↑ Erythropoiesis & ↑ Release of RBCs from bone marrow:

- In Cushing's disease (Hypercortisolemia) → Polycythemia.
- In Addison's disease (Hypocortisolemia) → Anemia.

b- ↑ Circulating P.M.N.L. by ↓ their migration from the circulation.

c- ↑ Platelet.

d- ↑ Coagulability of blood.

e- ↓ Lymphocytes → Lymphopenea (Catabolic effect on lymphoid tissues).

f- ↓ Eosinophils = Eosinopenea.

10- C. N. S.: Stimulation, Euphoria & psychological disturbances

11- Delays Wound Healing: Catabolic effect on fibroblast & connective tissue.

12- Uricosuric effect → ↑ Uric acid excretion.

13- Anti-Stress & Anti-Shock effect:

a- Hypernatremia → Hypervolemia → ↑ C.O.P. & ↑ Bl.p.

b- Hyperglycemia & ↑ Glycogen content in liver.

c- ↑ Sympatho-adrenal discharge.

d- C.N.S. stimulation → Sense of well being & adaptive effect to stress.

14- Anti-Vitamin D effect → ↓ Ca^{2+} absorption from G.I.T. → Hypocalcemia.

*Therapeutic Uses of Glucocorticoids:

NB) Types of Therapeutic Uses of Glucocorticoids:

1- Replacement Therapy in Adreno-Cortical Insufficiency (Addison's disease) → Use physiological doses → Almost NO adverse effects:
   a- Primary Addison's → Replace BOTH Gluco- & Mineralo-corticoid activities.
   b- Secondary Addison's (↓ ACTH) → Replace ONLY Glucocorticoid activity.
2- Supplementary & Suppressive therapy → Use pharmacological doses of drugs with powerful gluco- and minimal or no mineralo-corticoid activity → Many adverse effects.

1- Replacement Therapy in Adrenocortical Insufficiency (Addison's disease):

a- **Acute Addisonian Crisis**:
   - Cortisol 100 mg I.V. followed by I.V. infusion / 6 hours
   - Saline (0.9 % NaCl) + Glucose 5% ± Blood transfusion ± Vasopressors.

b- **Chronic Addison's Disease**:
   - Gluco.: Cortisone Acetate 25 – 37.5 mg/day Orally + Generous salt & sugar diet.
   - Mineralo.: DOCA (S.L., I.M., S.C. pellet implantation)
     or Fludrocortisone acetate (0.1-0.3 mg /day orally, most conventient).

2- Anti-Inflammatory:

a- Encephalitis, cerebral edema & ↑ Intra-cranial pressure.
b- Rheumatic carditis.
c- Chronic active hepatitis.
d- Nephritis & nephritic syndrome.
e- Arthritis: Rheumatic, Rheumatoid, Gouty & Osteoarthritis.

3- Immunosuppressive:

a- Auto-immune disease:
   - Collagen disease: Polymyositis, polyarthritis & systemic lupus erythematosis.
   - Blood diseases: Hemolytic & aplastic anemia, thrombocytopenia & agranulocytosis.
   - Inflammatory bowel syndrome e.g. ulcerative colitis.

b- Allergic diseases: Skin, eye & bronchial asthma.

c- Suppress tissue & organ rejection.

4- Suppress lymphoid tissues → Treat lymphoma & leukemia.

5- Suppress A.C.T.H. in adreno-genetal syndrome.

6- Suppress hypertrophic *scars & keloid* formation.

7- Shock & Stress conditions.

8- Hypervitaminosis D & Hypercalcemia.

*Adverse Effects of Glucocorticoids:

1- *Abrupt withdrawal after long use → Acute Addisonian Crisis.*
2- Iatrogenic Cushing's disease.
3- Hyperglycemia → Worsens Diabetes mellitus due to their Anti-Insulin effect.
4- Moon face & Buffalo hump.
5- Osteoporosis → Collapse of vertebrae & anemic fracture neck of femor.
6- Sublaxation of joints after repeated intra-articular injections.
7- Myopathy & muscle weakness.
8- Retardation of growth in children.
9- Teratogenicity.
10- Cataract & ↑ Intra-ocular pressure → Glaucoma.
11- Edema & weight gain.
12- Hypertension → May lead to Heart failure.
13- Hypokalemia → Worsens Digitalis toxicity.
14- Mask manifestations of bacterial & viral infections.
15- Immunosuppressant → ↑ Susceptibility to infection, flare up present infection & reactivation of latent T.B. lesion.
16- Peptic ulceration.
17- Thromboembolic manifestations.
18- Psychological disturbances.
19- Delays healing of wounds.
20 Anti-vitamin D → Hypocalcemia → Aggravate Osteomalacia & Osteoporosis.

* Contraindications Of Glucocorticoids:

1- *Abrupt withdrawal*
2- Cushing's disease.
3- Diabetes mellitus.
4- Osteoporosis.
5- Repeated intra-articular injections.
6- Hypertension & Heart failure.
7- Digitalis toxicity.
8- Uncontrolled infection.
9- Peptic ulcer.
10- Thromboembolic diseases.
11- Psychological disturbances.
12- During pregnancy.
13- Glaucoma.

*Precautions During Long Term Glucocorticoid Therapy:

1- *Gradual withdrawal.*
2-Test for glucose in urine
3- Routine X-ray spine.
4- Add anabolics.
5- Weight estimation.
6- Measure blood pressure.
7- Avoid in Digitalis toxicity.
8- Increase dose in stress.
9- Diet should by ***Rich*** in Proteins, K^+ & Ca^{2+} & ***Low*** in NaCl.

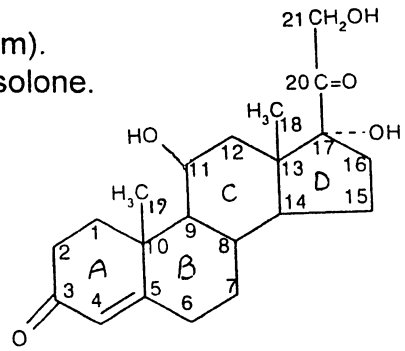
*Pharmacokinetics of Cortisol:

1- Well absorbed orally & Distributed all over the body.
2- Bound to plasma proteins mainly to Corticosteroids-Binding-Globulin (CBG = Transcortin) & albumin.
3- In liver: Inactive Cortisone ⟷ Active Hydrocortisone (Cortisol).
Conjugation with glucuronic acid & sulfuric acid → Excreted in urine.
4- t ½ of endogenous cortisol = 90 minutes.

*Structure-Activity Relationship of Corticosteroids:

Ring (A)

1- **The presence** of $C_4 = C_5$ double bond & $C_3 = O$ ketone group are essential for activity.
2- **Addition** of $C_1 = C_2$ double bond:
   a- ↑ Glucocorticoid activity & ↑ Duration of action (↓ Metabolism).
   b- *Examples*: Cortisone → Prednisone & Cortisol → Prednisolone.



Hydrocortisone (Cortisol)

Ring (B)

1- **Addition** of 6-α-Methyl:
   a- ↑ Both Gluco- & Mineralo- activity of Cortisol.
   b- ↑ Only Gluco-activity of Prenisolone.
2- **Addition** of 9-α-Florid → ↑ All biological activities.

Ring (C)

1- **The presence** of C_{11} – OH is essential for activity.
2- *Example*: Inactive Cortisone ($C_{11} = O$) → Active Hydrocortisone (C_{11} – OH).

Ring (D)

1- **The presence** of C_{17}-α-OH → Potent Glucocorticoid activity.
2- **The presence** of C_{21}-OH → Potent Mineralocorticoid activity.
3- **Addition of either C_{16}-CH_3 or -OH → Eliminate completely Mineralo- activity.**

*Preparations Of Commonly Used Corticosteroids:

A) Glucocorticoids:

Useful as Replacement, Anti-inflammatory & Immunosuppressant

1- Cortisone ($C_{11} = O$):
a- Inactive. Activated in liver into Hydrocortisone (C_{11} – OH).
b- Effective after systemic administration (Oral or Parenteral) BUT Not locally.

2- Hydrocortisone or Cortisol (C_{11} – OH).
- Active & effective after systemic & local administration.

3- Cortisone acetate suspension → Longer duration → Oral & I.M.

4- Cortisol acetate suspension → Longer → Oral, I.M. & Locally e.g. Intra-articular

5- Prednisone (Cortisone + $C_1 = C_2$):
a- Stronger & longer than cortisone as gluco-.
b- Must be activated in liver into Prednisolone. Effective after systemic & NOT local use.

6- Prednisolone (Cortisol + $C_1 = C_2$):
a- Stronger & longer than cortisol as gluco-.
b- Effective Oral, Parenteral & Local e.g. Intra-articular.

7- Methyl-Prednisolone → Stronger than Prednisolone as Gluco-.

8- Cortisol Na^+ Succinate
9- Cortisol Na^+ Phosphate
10- Prednisolone 21-Phosphate
} - Soluble → I.M. & I.V.
- In Emergency Acute Addisonian crisis, Status asthmaticus & Acute leukemia.

11- Beclomethasone → Inhalation in Bronchial asthma → Oro-pharyngeal moniliasis.

12- Fluorinated Corticosteroids:
a- Betamethasone → Similar to Beclomethasone.
b- Triamcinolone (Cortisol + $C_1 = C_2$ + C_9 - α - F + C_{16} - α - OH)
c- Dexamethasone (Cortisol + $C_1 = C_2$ + C_9 - α - F + C_{16} - α - CH_3)
} Pure Potent Gluco- with***out*** Minerlao-

B) Mineralocorticoids:

Useful in replacement therapy NOT Anti-inflammatory or Immunosuppressant

1- **Des-oxy-corticosterone Acetate (DOCA)**: S.L., I.M. & S.C. pellet implantation.
2- **Des-oxy-corticosterone Trimethyl Acetate**: I.M.
3- **Fludrocortisone acetate**: Orally, most convenient.

Corticosteroid	Gluco-	Mineralo-	Daily requirements
A) Short Acting (8 – 12 Hours):			
1- Cortisol	1	1	20 mg
2- Cortisone	0.8	0.8	25 mg
B) Intermediate Acting (12 – 36 Hours):			
1- Prednisone	4	0.8	5 mg
2- Prednisolone	4	0.8	5 mg
3- Methyl-Prednisolone	5	0.5	4 mg
4- Triamcinolone	5	NO	4 mg
C) Long Acting (36 – 72 hours):			
1- Betamethasone	25	NO	0.75 mg
2- Dexamethasone	25	NO	0.75 mg
D) Mineralocorticoids:			
1- Aldosterone	±	500	Not used
2- D.O.C.A.	NO	50	S.L. 2 – 6 mg
3- Fludrocortisone (12 – 36 hours)	10	125	Oral 0.1 – 0.3 mg

Adrenostatics

Drugs ↓ Adrenocortical activity → Useful in treatment Of Cushing's Disease

A) A.C.T.H. Dependent Cushing's:

1- **Cyproheptadine**: Antihistamine (H_1-blocker) + Anti-serotonin. } ↓ Release of A.C.T.H.
2- **Bromocriptine**: Direct dopamine agonist. }

B) A.C.T.H. Independent Cushing's:

1- Mitotane:

a- Destruction of adrenocortical cells.
b- Useful in Cushing's disease & Inoperable adrenocortical carcinoma.

2- Aminoglutethimide:

a- ↓ Conversion of Cholesterol → Pregnenolone (First step in steroidogenesis).
b- Useful in Cushing's syndrome.

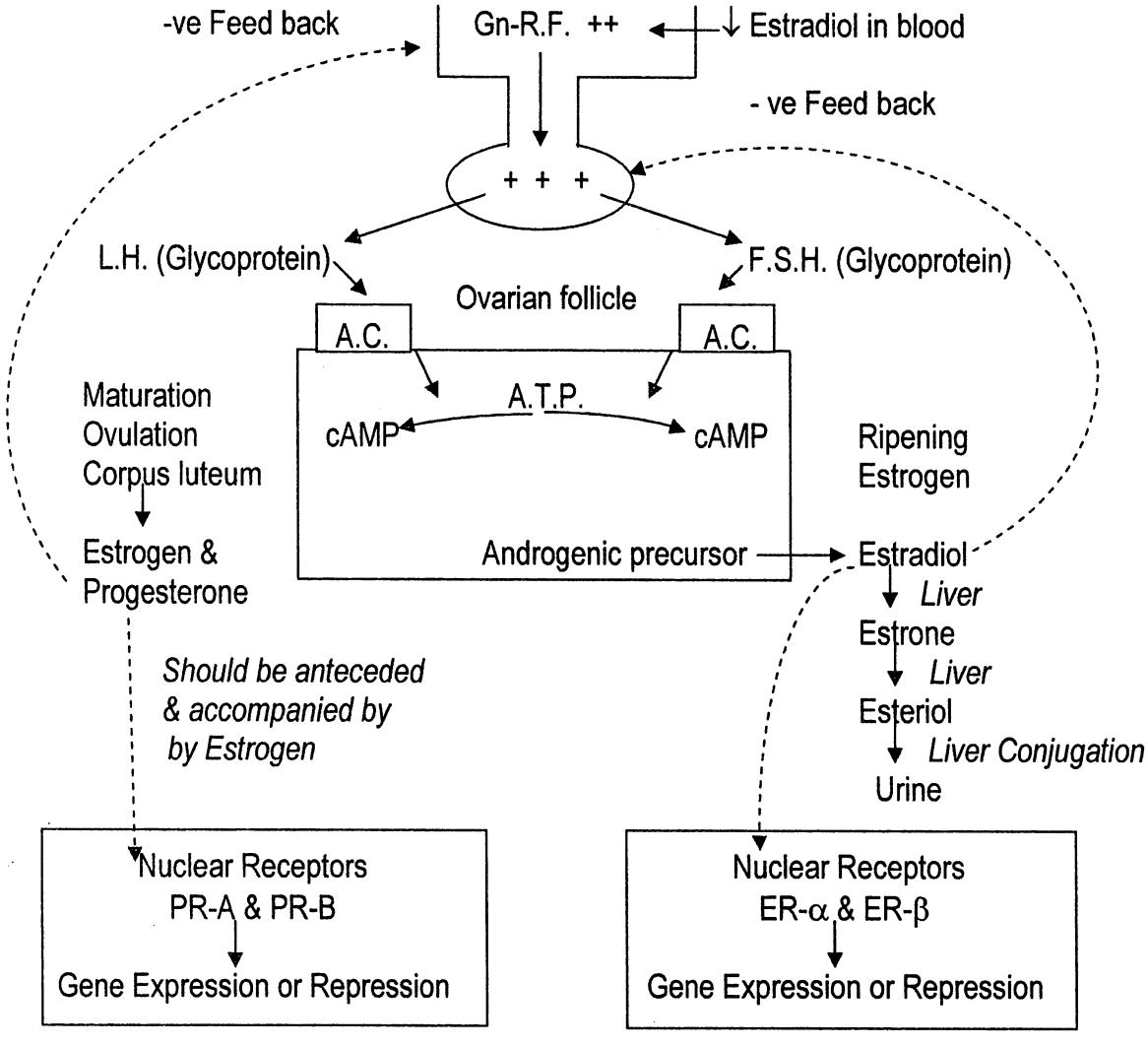
3- Ketoconazole:

a- Anti-fungal.
b- ↓ Conversion of Cholesterol → Pregnenolone (First step in steroidogenesis).
c- Useful in Cushing's disease.

4- Metyrapone (Mitopirone):

a- ↓ 11-β-Hydroxylase enzyme → ↓ Synthesis of BOTH Aldosterone & Cortisol → ↑ ACTH
c- ***Uses***: - Cushing's disease ± Aminolutethimide.
- Test the function of Anterior pituitary to secrete A.C.T.H.

Female Sex Hormones
Estrogens & Progesterone



I- Estrogens

1- Estradiol is the major & most powerful natural estrogen.
2- Synthesized under the effect of F.S.H. from Androgenic precursors.
3- The main sources are ovarian follicle, corpus luteum & placenta.
4- Small amounts are synthesized in Adrenal cortex, Testes, Liver, Fat, Sk.m.& Hair follicles.

NB) Follicle Stimulating Hormone (F.S.H.):

1- Decreased blood level of Estradiol stimulates the hypothalamus to secrete Gonadotrophin Releasing Factor (Gn.R.F.) = F.S.H.-R.F.
2- Gn.R.F. (F.S.H.-R.F.) stimulates the Anterior pituitary to secrete F.S.H.
3- F.S.H. (glycoprotein) stimulates a specific Membrane receptor on ovarian follicle →
↑ Adenylyl cyclase → ↑ cAMP →
a- Repining of ovarian follicle.
b- Synthesis of Estradiol from androgenic precursors.

* Pharmacokinetics of Estradiol:

1- Ineffective Orally due to extensive hepatic first pass metabolism.
Absorbed, also from the skin & mucous membranes.
2- In liver :
a-Estradiol is oxidized → Estrone (A weak estrogen).
b-Estrone is hydrated → Estriol (A weak estrogen).
c-All estrogens are conjugated with glucuronic & sulfuric acid.
3- Conjugated estrogens are excreted in urine. The urine does not contain free estrogens.

* Pharmacodynamics of Estrogens:

A) Mechanism of Action:

Estrogen, being steroid, gains access intra-cellularly passively → Combine with Nuclear Estrogen Receptors (ER-α & ER-β)→ Gene expression or Repression.

B) Actions of Estrogen:

1- Development of feminine **secondary sex** characters.
Breast → Promote duct system, stroma & fat.

2- **Female Genital Tract**: (NOT clitoris)
a- *Vagina* → Proliferation, cornification & ↑ Acid secretion.
b- *Cervix* → ↑ Water, sugar & Alkaline secretion → Wellbeing of sperms.
c- *Endometrium* → Proliferative phase.
d- *Myometrium* → ↑ Motility & ↑ Sensitivity to Oxytocin.

3- **Endocrine**:
a- *Females*:
1- Early phase of the cycle → ↓ FSH & ↓ L.H.
2- Mid-cycle: ↑ Estrogen → ↑ L.H. = L.H. surge → Ovulation.
3- Luteal phase → ↓ F.S.H. & ↓ L.H.
4- Exogenous Estrogen → ↓ FSH & ↓ LH → ↓ Maturation of the follicle → ↓ Ovulation → Contraceptive.
5- Large dose of Estrogen →↓ Prolactin → Suppress lactation.
b- *Males*: ↓ BOTH FSH & LH →
1- Atrophy of testes and prostate.
2- ↓ Testosterone secretion → Feminization.
3- ↓ Spermatogenesis → Infertility.
c- *↑ Plasma Globulin* → ↑ Binding of T_3 & T_4 → ↓ Free form → ↑ T.S.H. → Physiological goiter during pregnancy.

4- **Metabolism**:
a- *C.H.O.*: Hyperglycemia specially in diabetic & prediabetics.
b- *Fat*: ↑ HDL, ↓ LDL, ↑Triglycerides & ↓ Cholesterol.
c- *Protein*: Mild anabolic specially on female genital tract (Except clitoris).
d- *Bone*: ↓ Bone resorption. Closure of epiphyseal ends of long bones.

5- **↓ Sebaceous** gland activity.

6- **Na^+ & Water** retention.

7- **↑ Blood coagulability**: ↑ Factors II, VII, IX & X and ↓ Antithrombin *III*.

* Therapeutic Uses of Estrogens:

1- Replacement therapy to correct under-developed female secondary sex characters, BUT NOT Infertility.
2- Amenorrhea: Induction of an artificial cycle by withdrawal bleeding.
   NB) Abrupt withdrawal of estrogen at the end of an ***An***ovulatory cycle is the cause of menstruation.
3- As Hormonal Replacement Therapy (HRT) to prevent :
   a- Menopausal syndrome.
   b- Postmenopausal osteoporosis ± Calcitonin or Bisphosphonates.
   c- Senile atrophic vaginitis.
4- Vulvo-vaginitis.
5- Alone or with Progestins as Contraceptives.
6- Dysmenorrhea.
7- Dysfunctional uterine bleeding.
8- Suppression of postpartum lactation. Use estrogen LD immediately after parturition. **Bromocryptine** (Dopamine agonist) is better and safer.
9- Hirsutism
10- Acne vulgaris.
11- Atherosclerosis.
12- As an anabolic.
13- Cancer prostate in males.
14- Late postmenopausal cancer breast in females.

* Common Side Effects of Estrogen: *(See Contraception)*

1- **Nausea** & rarely vomiting.
2- **Sodium & water retention**:
   a- Headache & nervous tension.
   b- Enlarged tender breast.
   c- Edema & ↑ Body weight.
3- Intravascular **thrombosis**.

* Contraindications of Estrogen:

1- Estrogen-dependent neoplasms of breast and uterus.
2- Undiagnosed genital bleeding.
3- Liver disorders.
4- Thrombi-embolic diseases.

* Preparations of Estrogen:

A) Natural Estradiol (Steroid):

1- **Estradiol** → Not effective Orally. May be used topically & Transdermal patch in HRT
2- Estradiol Monobenzoate IM / 2-3 Days.
3- Estradiol Valerate in oil IM / 4 weeks.
4- Conjugated Estrogens = Permarin (Pregnant Mare urine): 50-100 ug/day po as HRT.

B) Semisynthetic Estrogen (Steroidal):

1- **Ethinyl Estradiol**: Most effective ORAL estrogen.
2- Mesteranol: Used in oral contraception.

C) Synthetic Non-Steroidal Estrogens :

1- **Diethyl Stilbesterol** : Useful Orally and parenterally.
2- Hexoesterol: Effective Orally.

* Anti-Estrogens = Selective Estrogen Receptor Modulators (SERM)

Synthetic Non-steroidal compounds that compete with estrogen for its receptors:

1- **Tamoxifen** *(Nolvadex)*: Used in Estrogen-dependent cancer breast in females.

2- **Clomiphene citrate** *(Clomid)*: Prevent estrogen-negative feed back on Pituitary → ↑ FSH & ↑ LH → An ovulation-inducing agent for infertility.

3- **Raloxifene:**
   a- *Estrogenic Effects*:
      - ↓ Bone reseorption → Prevent osteoporosis.
      - Improve lipid profile.
      - ↑ Venous thrombo-embolism.
   b- *Anti-estrogenic Effects*:
      - ↓ Risk of breast carcinoma.
      - Postmenopausal syndrome → Hot flushes.

II- Progestogens (Progestins)

Progesterone

- Steroid female sex hormone.
- Secreted from Corpus Luteum under the effect of L.H. Also secreted by the placenta.

* Luteinizing Hormone (L.H.):

1- Secreted by the Anterior pituitary in response to hypothalamic Gn-RF = L.H.-R.F.
2- L.H. (glycoprotein) → Bind to membrane receptor on an ovarian follicle primed by FSH → ↑ Adenylyl cyclase enzyme → ↑ cAMP →
   a- Complete the maturation of the follicle → Ovulation → Corpus luteum formation.
   c- Maintain the function of Corpus luteum to secrete Progesterone & Estradiol.

* Actions of Progesterone:

1- ***Mechanism of Action***: Similar to Estradiol. ↑ Nuclear Progesterone Receptors (PR-A & PR-B). It should be anteceded & accompanied by Estrogen. Estrogen up-regulates progesterone receptors.
2- -ve Feed back effect on Hypothalamic Gn-GF → ↓ FSH & LH. } Contraceptive.
3- Thick cervical mucus → ↓ Penetration by sperms. }
4- Endometrium → Secretory phase → Help implantation of fertilized ovum.
   NB) *Abrupt withdrawal of progesterone secreted by corpus luteum at the end of ovulatory cycle is the cause of menstruation.*
5- Maintains pregnancy:
   a- ↓ Uterine motility & ↓ sensitivity to oxytocin.
   b- ↓ T-lymphocytes → ↓ Rejection of fetus.
6- Vaginal epithelium is modified toward the condition of pregnancy.
7- Development of mammary gland acini.
8- Thermogenic.
9- Anti-Aldosterone effect.

* Preparations of Progestogens (Progestins):

A) Natural Progesterone: Not effective orally due to hepatic first pass metabolism. Very short duration after injection.

B) Synthetic Progestins:

- Resistant to hepatic metabolism.
- Effective orally.
- Long duration of action.

1- Progesterone Derivatives:

a- Examples:
- Hydrogeprogesterone caproate *(Primolut-depot)*
- Medroxyprogesterone *(Provera)*
- Megesterol

b- Selective progestational activity.
c- Suitable to maintain pregnancy & in contraception.

2- Nor-testosterone Derivatives:

a- Examples:
- Norethisterone *(Primolut-N)* - Norethindrone - Norethynodrel

b- They have some estrogenic & androgenic effects.
c- Not suitable to maintain pregnancy.
d- Used mainly in Contraception.

3- Norgestrel Derivatives:

a- Examples: Norgestrel, Levonorgestrel, Desogestrel & Norgestimate.
b- More potent progestin with little or no androgenic activity.
c- Useful in contraception.

* Therapeutic Uses of Progestins:

1- Alone or with Estrogen in Contraception.
2- Treat infertility if due to deficiency in progesterone.
3- Maintain pregnancy (Use progesterone derivatives).
4- Amenorrhea.
5- Dysmenorrhoea.
6- Dysfunctional uterine bleeding.
7- Endometriosis.
8- Endometrial carcinoma.
9- Premenstrual tension

* Anti-Progestogens:

1- **Mifepristone**.
2- Competes with progesterone for its receptor (partial agonist).
3- Sensitizes the uterus to the oxytocic effect of Prostaglanidins (PG).
4- Used for induction of abortion in first trimester. Single dose then followed by PG (Gemeprost intravaginal pessary or Misoprostol orally).

Contraception

1- Hormonal: Oral, Injectable, S.C. implant & intra-uterine.

2- Chemical:

1- Spermicidal agents e.g. Phenyl mercuric acetate.
2- Dosage forms: Cream, jelly, pessary & foaming tablet.
3- Applied into vagina 15-60 minutes before intercourse.

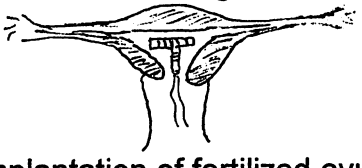
3- Mechanical;

1- Male condom.
2- Cervical cap.
3- Vaginal diaphragm.

} Better lubricated by spermicidal gel.

4- Intra-uterine Contraceptive Devices "Loops":

1- Loops (T-shaped) are impregnated with Barium to render them radio-opaque.
Two long threads are attached to the loop and extended into the vagina.



2- Types:
a- Loop impregnated with Progesterone.
b- Loops covered by copper.
3- Mechanism of Action:
a- Histo-biochemical changes in endometrium → ↓ Implantation of fertilized ovum.
b- ↑ Tubal & uterine motility → Expel the ovum.
c- Attract Macrophages → Phagocytosis of sperms & fertilized ovum.

5- Physiological Methods: Safety period.

6- Sterilization of males and/or females.

Hormonal Contraception

I- Injectable Contraceptives:

A) Progestogens:

1- ***Medroxyprogesterone acetate*** 150 mg I.M. / 3 months *(Depo-Provera).*
Start immediately after parturition. Does not affect lactation.
2- Adverse effects:
a- High incidence of failure.
b- Irregular bleeding or amenorrhea → May cause permanent infertility.

B) Estrogen + Progestogen:

1- **Estradiol valerate** 5 mg + **Norethisterone** 50 mg I.M. / Month *(Mesigyna).*
2- More effective than progestogen alone.
3- Adverse effects → Side effects of Estrogen + Affect lactation.

II- S.C. Implant:

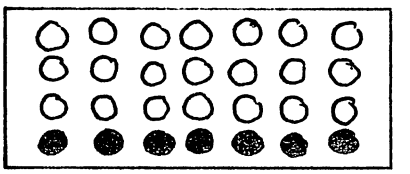
1- Progestogen e.g. **Levo-norgestrel** *(Norplant). Effective over several years.*
2- Dose Not affect lactation.

III- Oral Contraceptives

Use Synthetic hormones. Natural hormones are ineffective orally due to extensive hepatic first pass metabolism.

A) Combination Oral Contraceptives:

- Every pill contains Estrogen + Progestogen (Progestin).
- Start by the 5th day of the cycle for 21 days (3 weeks), then rest for 7 days (a week) or take iron during this week.



1- Monophasic Pills:

Each pill contains the same amount of estrogen + progestin.

A- High dose Estrogen + High dose Progestin *(Primovlar):*

1- Estrogen (0.05 mg Ethinyl Estradiol) + Progestin (0.5 mg Norgestrel).
2- 100% efficacy.
3- If the lady forgets one pill, she takes 2 pills on the next night.
4- High dose estrogen → Nausea, edema & may be thrombosis.

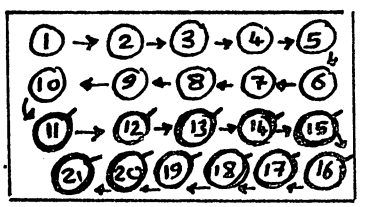
B- Low dose Estrogen + Low dose Progestin *(Microvlar):*

1-Estrogen (0.03 mg Ethinyl Estradiol) + Progestin (0.15 mg Levonorgestrel).
2-100 % efficacy.
3-Low estrogen → Less side effects BUT Omission of one pill → Loss of protection.
Low progestin → Spotting & break-through bleeding.

C- Low dose Estrogen + High dose Progestin *(Loestrin)*:

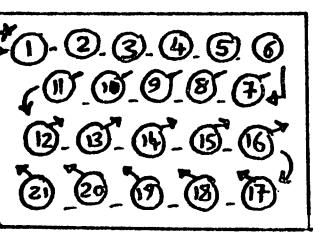
1- Estrogen (0.03 mg Ethinyl Estradiol) + Progestin (1.5 mg Norethindrone).
2- 100% efficacy.
3- Low estrogen → Less side effects BUT Omission of one pill → Loss of protection.
High progestin → LESS Spotting & break-through bleeding.

2- Biphasic Pills:



1- Days 1 - 10 : Ethinyl Estradiol 0.035 mg + Norethindrone 0.5 mg.
2- Days 11 - 21 : Ethinyl Estradiol 0.035 mg + Norethindrone 1.0 mg.
3-Advantages:
a-Less estrogen → Less side effects.
b-Increasing Progestin → Less spotting or break-through bleeding.

3- Triphasic Pills *(Triovlar):*



a- Pills are taken according to the following schedule :
- First 6 days (Brown pills) → Low Estrogen (30 ug Ethinyl Estradiol) + Low Progestin (50 ug Levonorgestrel).
- Then 5 days (White pills) → More Estrogen (40 ug) + More Progestin 75 ug).
- Then 10 days (Yellow pills) → Less Estrogen (30 ug) + Still more Progestin (125 ug).

b- Advantages:
- Less Estrogen → Less side effects.
- Increasing Progestin → Less spotting & break through bleeding.

NB) During Combined pill therapy menstruation is suppressed due to daily administration of progestin. Bleeding occurs ONLY after stop of the pill.

B) Sequential Method:

1- Start by Estrogen ALONE for 14-16 days, then COMBINATION of Estrogen + Progestin for 5-6 days.
2- More physiological BUT success about 98-99%

C) Minipill (Small dose of Progestin Alone)

1- Small dose of Progestin ALONE. NO estrogen → Almost NO side effects.
Examples: *Microlut (30 ug Levonorgestrel) & Micronor (350 ug Norethindrone).*
2- Pills are taken EVERY DAY without interruption.
3- Does NOT inhibit ovulation.
4- Does NOT inhibit the cycle. Menstruation occurs BUT irregular.
5- Does NOT inhibit lactation. Preferred oral contraception for lactating mothers.
6- Success rate about 97-98%. If amenorrhea more than 60 days → Do pregnancy test.

D) Post-coital or Morning-After Pills

1- They are used rarely e.g. after rape.
2- Start therapy within 72 hours after rape.
3- Methods:
   a- Large dose of estrogen Only: Diethyl Stilbesterol 25 mg bid PO for 5 days.
      Continue treatment despite nausea and vomiting.
      If failed → Do surgical abortion. It may cause cancer vagina in female offspring.
   b- Large dose Progestin Only
   c- Ethinyl estradiol 100 ug + Norgestrel 1 mg two doses in 12 hours.
   d- Mifepristone 600 mg OD PO ± Prostaglandin (Misoprostol PO or Gemeprost vaginal pessary).

* *Mechanism of Action of Hormonal Contraception:*

A) Estrogen:

1- Most important item in hormonal contraception.
2- ↓ F.S.H. → ↓ Follicle growth → ↓ Ovulation.
3- Postcoital pills (Large dose of Estrogen):
   a- ↑ Motility of oviduct & endometrial changes → ↓ Fertilization & Implantation.
   b- Withdrawal bleeding → Expel fertilized ovum.

B) Progestin:

1- Used mainly with estrogen:
   a- Physiological withdrawal bleeding.
   b- ↓ Risk of estrogen-induced neoplasms in ovary, endometrium or breast.
   c- ↓ Premenstrual tension & dysmenorrhea.
   d- Symptomatic relief of endometriosis if present.
   e- Help in contraception:
      - ↓ Gn-RF → ↓ FSH & LH → ↓ Ovulation.
      - Thick cervical mucus → ↓ Penetration of Sperms.
2- Progestins in sufficient large dose → ↓ The cycle → No menstruation.
3- Very large dose of Progestins e.g. Injectable Medroxyprogesterone 1000 mg → Ovarian & endometrial atrophy.

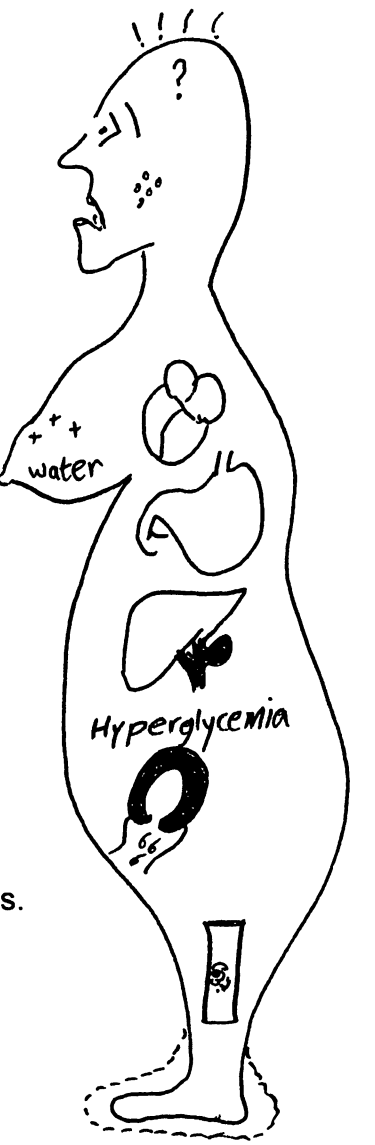
4- Small doss of Progestin e.g. Minipill:
a- Does NOT inhibit ovulation.
b- Does NOT inhibit the cycle → Menstruation BUT irregular.
c- Does NOT inhibit lactation.
d- Mechanism of Contraception → Thick cervical mucus & endometrial changes.

C) Combined Estrogen + Progestin:

1- Inhibit release of BOTH F.S.H. & L.H.
2- Inhibit coordinated motility uterus body & fallopian tubes → Altered transport of sperm & fertilized ovum.
3- Altered endometrium → ↓ Implantation of fertilized ovum.

*Adverse Effects of Hormonal Contraceptives:

Most of the adverse effects are due to Estrogen



1- C. N. S.:
a- Vascular headache (Migraine) b- Irritability.
c- Loss of libido d- Depression

2- Skin:
a- Pigmentation (Chloasma) b- Loss of hair
c- Acne may improve (Estrogen) or worsen (Progestin)

3- C. V. S.:
a- Hypertension.
b- Thrombo-embolism e.g. Deep venous thrombosis.
Especially in obese, heavy smoker & over 35 years.

4- Fluid Retention:
a- Enlarged tender breast (Mastalgia).
b- Weight gain, also due to anabolic effect.

5- Inhibition of Lactation

6- G. I. T. → Nausea & occasional vomiting.
a- Shift to less estrogenic pills.
b- If persistent → Do pregnancy test.

7- Hepato-biliary dysfunction → Stasis of bile & gall stones.

8- Hyperglycemia.

9- Uterine bleeding *(Due to LOW Progestin):*
a- Spotting = Minimal bleeding during pill treatment.
Continue intake of pills But double the dose.
b- Break-through bleeding = Menstruation during pill treatment.
Stop intake of pills for a week. Start new cycle using pills with MORE progestin.

10- Hypomenorrhea & even Amenorrhea:
Stop intake of pills. If still amenorrhea → Use anti-estrogen e.g. Clomiphene.

11- Leucorrhoea due to cervical erosion & monilial infection.

*Contraindications of Pills:

1- C.N.S.: Vascular headache e.g. Migraine.
2- C.V.S.: Heart failure, Hypertension & history of thrombo-embolism
3- Women *over 35* years especially *Obese* and/or heavy *Smokers*.
4- Breast tumors e.g. fibro-adenoma & carcinoma.
5- Hepato-biliary dysfunction e.g. history of jaundice or gall stones.
6- Diabetic & Prediabetic patients.
7- Uterine tumors e.g. Fibroids.

*Drug Interactions of Pills:

A) Drugs ↓ Effect of Pills:

1- Hepatic microsomal enzyme inducers e.g. Phenobarbital, Phenytoin, Carbamazepine, Rifampicin & Tobacco smoking.
2- Liquid paraffin → ↓ Absorption of pills.

B) Pills ↓ Effect of Other Drugs:

1- Anti-coagulants.
2- Anti-diabetics.
3- Anti-hypertensives
4- Anti-dyslipidemics

C) Drugs ↑ Adverse Effects of Pills:

Anti-fibrinolytics & tobacco smoking → ↑ Incidence of thrombo-embolism.

*Uses of Contraceptive Pills:

1- Contraception.
2- Pregnancy test: 2 pills / day for 5 days then stop → If withdrawal bleeding → No pregnancy.
3- Suppression of lactation: 3 pills/day for 7 days. Bromocriptine (D_2-agonsit is better).
4- Amenorrhea: Induction of artificial cycle.
5- Dysmenorrhea.
6- Dysfunctional uterine bleeding.
7- Endometriosis (Large dose of Progestins).
8- Postpone menstruation.

NB) Contraception in Men:

Still under trial & Not as effective as those in women.

1- Testosterone.
2- Testosterone + Levonorgestrel.
3- Gossypol (cottonseed derivative) → Affect seminiferous epithelium.

Treatment of Infertility

A) Gonadotrophins:

1- Effective in patients with hypothalamo-pituitary lesion BUT normal functioning ovary.
2- Start by F.S.H. then L.H.
3- Use human gonadotrophins. Animal gonadrophins are antigenic.

B) Anti-Estrogens:

1- **Clomiphene citrate** 50 mg/day for 5 days.
2- Compete with estrogen for its nuclear receptors → ↓ -ve feed back effect of estrogen on hypothalamus & anterior pituitary → ↑ F.S.H. & L.H.
3- effective in patients with normal hypothalamo-pituitary function & normal & functioning ovary.
4- Adverse effects → Enlarged cystic ovary & multiple twins.

C) Progestins in patients with defective secretory phase of endometrium.

D) Bromocriptin

1- Direct Dopamine D_2-receptor agonist → ↓ Secretion of Prolactin.
2- Effective in patients with hyperprolactinemia = Galactorrhea-Amenorrhea syndrome.

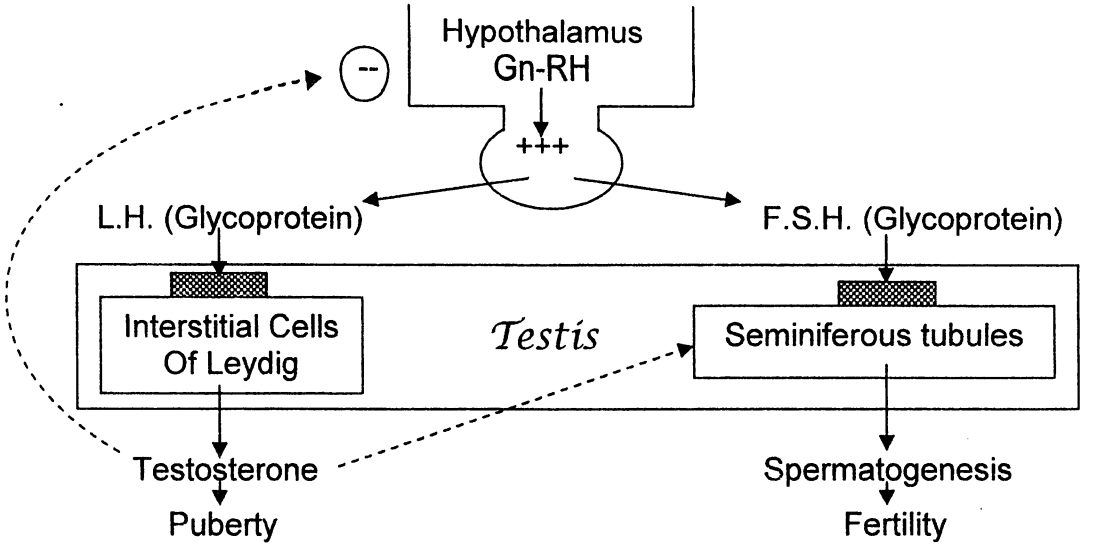
Androgens

Testosterone

1- Testosterone is the natural male sex hormone. It is synthesized and secreted from Interstitial cells of Leydig in the testis under the control of L.H.
2- Other weaker androgens are secreted from Adrenal cortex (Under control of ACTH) & the ovary.

* Mechanism of Action:

1- *Steroid* → ↑ Specific intracellular Androgenic Receptors → Affect Gene expression.
2- In *Prostate*, Seminal vesicles, Epididymis & Skin:
Testosterone (Inactive) $\xrightarrow{5\text{-}\alpha\text{-}Reductase\ Enzyme}$ Dihydrotestosterone (Active).
3- In *Skeletal muscle* & Bone marrow, testosterone is active by itself or converted to another active metabolite.
4- *Pseudohermaphroditism*, either due to:
   a- Deficiency of 5-α-Reductase enzyme → Male hypogonadism BUT well developed skeletal muscles. Treatment by Dihydrotestosterone.
   b- Deficiency of testosterone receptors → Male hypogonadism + Underdeveloped Sk.m. → Feminization. No medical treatment. Conversional surgery may be needed.



*Pharmacological Actions of Testosterone:

1- Development of Male secondary sex characters & growth of genitalia → Puberty.
2- Testosterone + F.S.H. → Seminiferous Tubules → Spermatogenesis → Fertility.
But Testosterone Alone in large dose → ↓F.S.H. & ↓L.H. → ↓ Spermatogenesis.
3- ↑ Libido in males & females.
4- Anabolic.
5- Closure of epiphyseal ends of long bones.
6- Na^+ & Water retention.

*Therapeutic Uses of Testosterone:

1- Replacement therapy in Male Hypogonadism = Delayed Puberty:
   a- If testicular disorder → Give Testosterone → Restores Puberty *But Not* fertility.
   b- If Pituitary disorder *But* normal & functioning testis → Give L.H. + F.S.H. → Restore puberty & fertility.
2- To check excessive linear growth.
3- With Estrogen in menopausal syndrome → ↓ Excess release of Gonadotrophins & Anabolic & ↓ Osteoporosis.
4- Pre-menopausal Cancer Breast. Testosterone → Anti-Estrogen & ↓ Gonadotrophins.

*Adverse Effects of Testosterone:

1- Aggravate cancer prostate.
2- Musculanization in Female patients.
3- Na^+ & H_2O retention.
4- Cholestatic jaundice especially *Methyl-testosterone.*

*Contraindication → Cancer Prostate.

*Preparations of Testosterone:

1- Natural Testosterone → Not effective orally due to extensive hepatic first pass effect.
2- Testosterone S.C. implant.
3- Testosterone propionate in oil → I.M.
4- ***Methyl-Testosterone*** → Sublingual.
5- ***Fluoxymesterone*** → Potent Oral semi-synthetic androgen.

*Anti-Androgens:

A) Cyproterone (Androcur) & Flutamide (Eulexin):

1- Steroids that *compete* with testosterone for its intracellular receptors
2- Therapeutic Uses:
   a- Cancer prostate
   b- Precocious puberty
   c- Hyper-sexuality
   d- Male baldness
   e- Cane
   f- Female hirsutism & virilization

B) Finasteride (Nopecia, Proscure):

1-Mechanism: ↓ 5-α-Reductase enzyme.
2- Therapeutic Uses: Similar to Cyproterone.

NB) Danazol (Danol):

1- Modified Progestogen with weak androgenic activity.
2- ↓ Mid-cycle surge of Gonadotrophins. } Useful in Endometriosis, menorrhagia
3- ↓ Steroidogenesis & ↓ Spermatogenesis. } & gynecomastia.
4- ↑ Synthesis of Anti-hemophilic globulin → Useful in Hemophilia.

Anabolic Steroids

1- Derivatives of Testosterone → Anabolic activity > Androgenic effects.
2- Anabolic → +ve Nitrogen & +ve Calcium balance.
3- Therapeutic Uses:
   a- Senile osteoporosis
   b- Aplastic anemia
   c- After major surgery
   d- ↓ Protein catabolism → Delays uremia in Renal failure
4- Side Effects → Musculanization in Female patient & fetus.
5- Contraindication → Cancer prostate.
6- Preparations e.g. Nandrolone *(Decadurabolin) I.M.*

Pituitary Hormones

All pituitary hormones are Polypeptide & Glyco-proteins →
1-Not effective orally.
2-They bind to specific membrane receptors → ↑ Adenylyl cyclase → ↑ cAMP.

*Types of Pituitary Hormones:

A) Anterior Pituitary Hormones:

1- They are synthesized, stored & released from Anterior pituitary cells.
2- *Basophil cells* → T.S.H., A.C.T.H., F.S.H. & L.H.
   Acidophil cells → Prolactin & Growth hormone.
3- They are under control of Hypothalamic releasing factors,
   Except Prolactin → Under control of Inhibitory factor = Dopamine (D_2-receptors).
   In Hypothalamic lesion → ↓ ALL pituitary hormones BUT ↑ Prolactin secretion.
4- Hypothalamic releasing factors are under –ve feed back effect of circulating hormones.

B) Posterior Pituitary Hormones:

1- Synthesis in Hypothalamic Supra-optic & Para-ventricular nuclei.
2- Storage & release from posterior pituitary.
3- *Examples*: Oxytocin & Vasopressin (A.D.H.) → Both are Nonapeptides (9 amino-acids).

Anterior Pituitary Hormones

I- Growth Hormone (G.H.):

1- Polypeptide hormone composed of 188 amino-acids.

2- Under control of hypothalamic hormones:
   a- Growth hormone releasing-hormone.
   b- Growth hormone release-inhibiting hormone = **Somatostatin**.

3- May act through release of Hepatic peptide (**Somatomedins** = Sulfation factor).

4- ↑ Growth of soft tissues & bones:
   a- No effect on growth of brain & eye ball.
   b- Over production:
      - Before closure of epiphyseal ends of long bones → **Gigantism**.
      - After closure of epiphyseal ends of long bones → **Acromegaly**.
   c- Under production → Pituitary **Dwarfism**. Treated by ***Human*** Growth Hormone.

5- *Metabolic actions*:
   a- Anabolic → +ve Nitrogen & +ve Calcium balance.
   b- Fat → ↑ Lipolysis → Lipemia.
   c- Carbohydrates → Anti-Insulin → Hyperglycemia.

II- Prolactin (Leuto-Trophic Hormone = L.T.H.):

1- Glycoprotein synthesized, stored & secreted by Anterior pituitary Acidophil cells.

2- Responsible for lactation. Needs the presence of physiological amounts of Estrogen, Progesterone, Cortisol & Insulin.

3- Under control of Hypothalamic-Inhibitory factor = Dopamine (D_2-receptors).
   If hypothalamic lesion → ↑ Prolactin.

4- Drugs → ↓ Dopamine D_2-activity → ↑ Prolactin → Galactorrhea-amenorrhea syndrome & they also worsens Parkinsonism:
   a- Anti-psychotics → Block D_2-receptors:
      - Phenothiazines e.g. Chlorpromazine.
      - Butyrophenones e.g. Haloperidol.
      - Thioxanthenes e.g. Zuclopenthixol.
   b- Anti-emetics e.g. Metoclopramide.
   c- Sympathoplegics e.g. Reserpine (Depletion) & α-Methyl-Dopa (↓ Synthesis).
   d- Cimetidine (H_2 – Histamine receptor blocker).

5- Treatment of Hyperprolactinemia = Galactorrhea-amenorrhea syndrome:
   Dopamine D_2-Agonists e.g. L-Dopa (Prodrug → Dopamine) & Bromocriptine.

III- Thyroid Stimulating Hormone (T.S.H. = Thyrotropin):

1- Glycopotein hormone of Anterior pituitary basophil cells.
2- ↑ Size, vascularity & function of Thyroid gland to secrete Thyroid hormone (T_3 & T_4).
3- Therapeutic Uses:
   a- To differentiate between primary (Thyroid) & secondary (Pituitary) hypothyroidism.
   b- ↑ Uptake of radio-active ^{131}I by metastatic malignant thyroid tissue.
4- Thyroid Stimulating Immunoglobulin (T.S.I. = Long Acting Thyroid Stimulator) is an immunoglobulin released by lymphocytes → ↑ T.S.H. receptors → Hyperthyroidism.

IV- Adreno-Cortico-Trophic Hormone (A.C.T.H. = Corticotropin):

1- Polypeptide hormone composed of 39 amino-acids.
2- ↑ Size, vascularity & function of Zonae fasiculata & reticularis → Synthesis & secretion of Cortisol & Androsterone.
3- Therapeutic Uses:
   a- To differentiate between primary (Adrenal cortex) & secondary (Pituitary) Addison's.
   b- Same indications of Cortisol *Except* Primary Addison's disease.
   c- To facilitate withdrawal of glucocorticoids after their long use.
4- Preparations:
   a- Corticotrophin (A.C.T.H.) I.M. & S.C.
   b- Synthetic Tetracosactrin "*Synacthen*" → First 24 amino acids of A.C.T.H. → Same effect of A.C.T.H. & less antigenic → Snuff, I.M. & S.C.

V- Follicle Stimulating Hormone (F.S.H.):

1- Glycoprotein synthesized, stored & secreted by Anterior pituitary basophil cells.
2- In Females → Ripening of Ovarian follicle + Synthesis & release of Estradiol.
   Useful in treatment of Infertility due to Hypothalamo-pituitray lesion BUT Normal ovary.
3- In Males → F.S.H. + Testosterone → Spermatogenesis → Fertility.
   Useful in treatment of Infertility due to Hypothalamo-pituitary lesion BUT Normal Testis.

VI- Luteinizing Hormone (L.H. = Interstitial Cell Stimulating Hormone):

1- Glycoprotein synthesized, stored & secreted by Anterior pituitary basophil cells.
2- In Females → Maturation of ovarian follicle, ovulation & maintain Corpus luteum → Estradiol & Progesterone.
   Useful in treatment of Infertility due to Hypothalamo-pituitray lesion BUT Normal ovary.
3- In Males → Testosterone secretion → Puberty. Useful in treatment of Delayed puberty (Male hypogonadism) due to Hypothalamo-pituitray lesion BUT Normal Testis.

NB)

1- Human Menopausal Gonadotrophins (H.M.G.)→ Obtained from urine of menopausal women → Has F.S.H. + L.H. activities.
2- Urofollitropin → Obtained fro urine of menopausal women → F.S.H. activity.
3- Human Chorionic Gonadotrophins (H.C.G.) → Secreted by placenta → Obtained from urine of pregnant women → Has L.H. activity.

Posterior Pituitary Hormones

I- Oxytocin (Pitocin)

* Nature & Source:

1- Polypeptide (Nonapeptide = 9 Amino acids) hormone:
   a- Not effective orally.
   b- ↑ Membrane receptors → ↑ Adenylyl cyclase → ↑ cAMP.

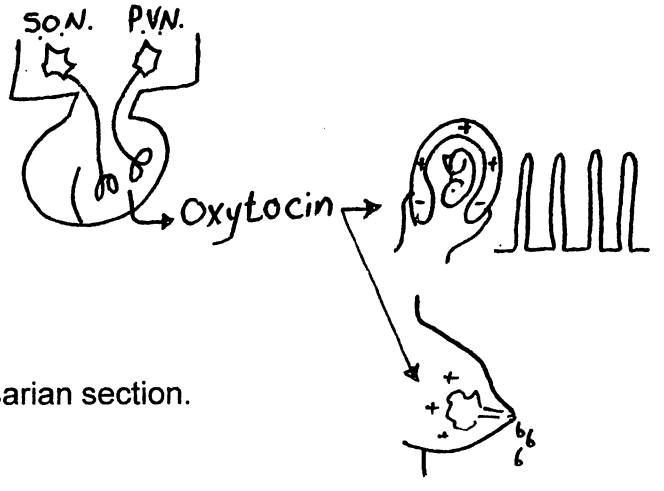
2- Synthesis by Hypothalamic Supra-optic & Paraventricular nuclei.

3- Storage & release from Posterior pituitary gland.

*Pharmacological Actions:

1-Physiological Uterine contractions → Oxytocic:
a- Contracts the fundus & relaxation & effacing of the cervix..
b- Rhythmic contractions.
c- ↑ by Estrogen & ↓ by Progesterone.

2- Contraction of Myo-epithelial cells in mammary acini → Ejection of Preformed milk.



*Therapeutic Uses:

1- Induction of labor & abortion.
2- Uterine inertia.
3- Prevent & treat post-partum hemorrhage.
4- Breast engorgement by milk.

*Side Effect → Rupture of uterus IF:

1- Cephalo-Pelvic disproportion.
2- Presence of a uterine scar from previous Caesarian section.

*Preparations:

1- Natural oxytocin I.M. & I.V.
2- Synthetic Oxytocin = ***Syntocynon*** I.M., I.V. & Nasal spray

*Ocytocic Drugs:

1- Oxytocin & Syntocynon I.M. & I.V. to induce LABOR & Abortion.

2- PG E_2 & F_{2a}:
   a- Physiological uterine contractions similar to oxytocin.
   b- Used (± Antiprogesterone = Mipepristone) to induce ABORTION & labor.

3- Ergometrine (= Ergonovine) & Methyl-Ergometrine *(Methergin)*:
   a- Non-physiological titanic contractions of A LL uterine segments.
   b- Used AFTER delivery of fetus & placenta to:
      - Prevent & treat pot-partum hemorrhage
      - Help involution of the uterus

4- Quinine & Quinidine → Contraindicated in pregnancy → Abortion.

*Uterine Relaxants = Tocolytic Agents:

A) Examples:

1- Sympathomimetics β_2-Agonists: Ritodrine, Isoxsuprine & Salbutamol.
2- Calcium Channel Blockers e.g. Verapamil
3- Nitrites and Nitrates.
4- N.S.A.I.D. e.g. Indomethacin → ↓ C.O.X. → ↓ Synthesis of PG.

B) Therapeutic Uses:

1- Dysmenorrhea
2- Threatened abortion & Premature labor.
3- Contraction ring of uterus during labor.

II- Anti-Diuretic Horone = Vasopressin (A.D.H. = Vp)

* Nature & Source:

1- Polypeptide (Nonapeptide = 9 Amino acids) hormone:
   a- Not effective orally.
   b- ↑ Membrane receptors → ↑ Adenylyl cyclase → ↑ cAMP.
2- Synthesis by Hypothalamic Supra-optic & Paraventricular nuclei.
3- Storage & release from Posterior pituitary gland.
4- ↑ Release of A.D.H. by:
   a- ↑ Osmotic pressure of blood → ↑ Hypothalamic osmo-rceptots.
   b- Drugs: Nicotine, Morphine, Barbiturates & Ether.
   c- Stress.
5- ↓ Release of A.D.H. by:
   a- ↓ Osmotic pressure of blood e.g. Drinking water.
   b- Drugs e.g. Ethyl alcohol (No tolerance for this action).

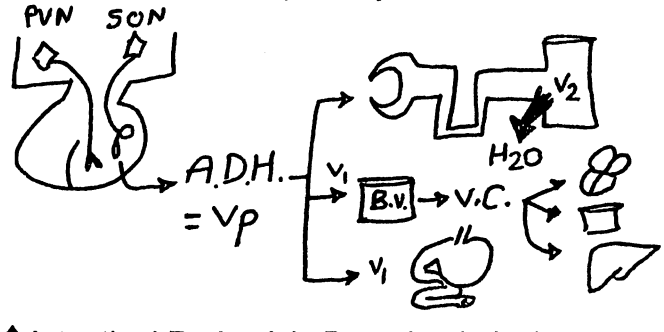
*Pharmacological Actions of A.D.H.:

A) Small Physiological Dose:

1- Anti-Diuretic effect → ↑ V_2-receptors → ↑ Water reabsorption from D.C.T. & Collecting tubules to Medulla of the kidney = Part of Counter-Current Multiplier System.
2- No significant role in control of normal Bl.p.

B) Large Pharmacological Doses:

1- Anti-Diuretic Effect (↑ V_2-receptors).
2- Generalized V.C. (↑ V_1-Receptors):
   a- Coronary V.C. → Angina pectoris.
   b- Peripheral V.C. → ↑ Systemic Bl.p.
   c- Mesenteric V.C. → ↓ Portal Bl.p.
3- Spasmogenic effect on smooth muscles → ↑ Intestinal Peristalsis But tahyphylaxis.



*Therapeutic Uses of A.D.H.:

1- Diagnosis & Treatment of Hypothalamo-pituitary **Diabetes Insipidus**.
2- Portal hypertension & bleeding **Esophageal varices**.
3- **Paralytic ileus**.

*Preparations:

1- Desiccated Posterior Pituitary Powder → Snuff → Atrophic rhinitis.
2- Vasopressin aqueous solution I.M. → Rapid acting.
3- Vasopressin tannate Oily suspension I.M. → Long acting.
4- **Lypressin** (Lysine-Vasopressin) Nasal spray.
5- **Desmopressin** acetate Nasal spray & I.M.

NB) Diabetes Insipidus:

A) Hypothalamo-Pituitary Diabetes Insipidus:

1- Causes: ↓ A.D.H.
a- Hypothalamic lesion → Permanent deficiency of A.D.H.
b- Pituitary lesion → Temporary deficiency of A.D.H. → Then Normal.

2- Treatment:
a- A.D.H. (Desmopressin).
b- Chlorpropamide: 1st generation Long acting Sulfonylurea Oral Hypoglycemic.
c- Carbamazepine: Anti-epileptic.
d- Clofibrate: Anti-dyslipidemic drug.

B) Nephrogenic Diabetes Insipidus:

1- Cause: Insensitivity of Nephron to circulating A.D.H.
2- Treatment by Thiazide diuretics → ↓ R.B.F. & ↓ G.F.R.

NB) A.D.H. Antagonists:

Useful in treatment of Syndrome of Inappropriate A.D.H. Secretion (S.I.A.D.H.) → Chronic hyponatremia.

1- **Lithium carbonate** → Mood stabilizing Anti-Manic drug.

2- **Demeclocycline** → Tetracycline antibiotic.

3- **Methoxyflurane** → General anesthesia.

*Chemical Classification Of Hormones:

1- Steroid hormones: Adrenocortical & ex hormones.
2- Non-Steroidal Hormones:
   a- Polypeptides & Proteins: Pituitary, pancreatic, GIT hormones, Calcitonin & P.H.T.
   b- Amino-acid Hormones:
      - Tryptophane derivatives: Serotonin & Melatonin.
      - Tyrosine derivatives: Thyroid hormones & Catecholamines.

*Physico-Chemical Properties:

1- Steroid & Thyroid hormones → Lipid-soluble → Gain access Intra-cellularly.
2- Others → Not lipid soluble.

*Types of Hormone Receptors:

1- Membrane receptors → Usually linked to G-protein → Affect Adenylate cyclase, Guanylate cyclase or Phospholipase enzymes.
2- Intra-cellular receptors:
   a- Cytoplasmic receptors e.g. Glucocorticoid-receptors.
   b- Nuclear receptors e.g. Estrogen receptors.
   c- Others e.g. Mitochondrial receptors.

*Mechanism Of Action Of Hormones:

A) Steroid & Thyroid Hormones:

1- Lipophilic → Gain access intra-cellulary passively → Affect **Nuclear receptors** either directly or through activation of cytoplasmic receptors → **Gene** expression or repression
2- Their effect needs hours-to-days to be manifested.

B) Other Hormones:

1- Not lipophilic.
2- They bind to membrane receptors linked to G-protein:
   a- ↑ Adenylate cyclase → ↑ camp → Phosphorylation of intracellular proteins → Enzyme activation or inhibition. The effect appears usually rapidly within minutes. These actions are potentiated by Methyl-xanthines e.g. Aminophylline (↓ P.D.E.).
   b- ↓ Adenylate cyclase enzyme → ↓ cAMP e.g. Insulin → Anti-lipolytic.
   c- ↑ Guanylate cyclase → ↑ cGMP.
   d- ↑ Phospholipase C → ↑ IP_3 & DAG → ↑ Ca^{2+} + Calmodulin → ↑ Protein kinases.
3- Insulin receptor ($2\alpha + 2\beta$ subunits connected together by bisulfide bonds) is linked directly to Tyrosine-kinase enzymes → Phosphorylation of intracellular proteins, enzymes & translocation of Glut-4 → Then Insulin-receptor complex is internalized → Metabolism of insulin → Recycling of the receptor.

C) Cell Membrane Permeability:

1- Insulin → ↑ Glucose + K^+ + Ca^{2+} + Phosphate uptake by sensitive tissues.
2- A.D.H. → ↑ Permeability to water in D.C.T. & Collecting tubules of the Nephron.

Chemotherapy

ANTIMICROBIALS

- These are drugs used in treatment of infectious diseases whether bacteria, viral, fungal or parasitic.
- They either kill (= cidal) or inhibit the growth (= static) microorganisms in high dilutions and with minimal harm to the host.
- They may be obtained from living microorganisms e.g. fungi (= Antibiotics) or synthetic.

Anti-bacterial Anti-Microbials

I- β-Lactam Antibiotics

(Penicillins, Cephalosporins, Monobactams & Carbapenems)

* Anti-Bacterial Activity :

1- Bactericidal Antibiotics.
2- They bind to specific Penicillin-Binding-Protein (PBP), at least 7 types :
   a- ↓ Transpeptidase enzyme responsible for cross-linking of peptidoglycans, a final step in cell wall synthesis → ***↓ Cell Wall Synthesis***.
   b- Activate Autolytic enzymes (Autolysins) → Lysis of cell wall.
   c- Bacteria imbibe water due to its interior high osmotic pressure → Rupture and DEATH of the microbe.
   d- They affect mainly growing bacteria rather than resting one.
3- Selectivity: Human cells do not contain peptidoglycan cell wall.
4- Resistance:
   a- Natural absence of peptidoglycan cell wall e.g. Mycoplasma.
   b- Plasmid Mediated:
      - Production of β-lactamase enzymes (Too many types). Some of them are specific penicillinases & cephalosporinases.
      - Alteration in the PBP.
      - Decreased permeability to antibiotics.

I- PENICILLINS

* Derivatives of 6-Aminopenicillanic acid.
* They contain β-lactam ring which is essential for the anti-bacterial activity.
* Obtained naturally from penicillium molds and semi-synthetically.

* Members of Penicillins:

1- Benzyl Penicillin (Penicillin G):

1- Natural penicillin.
2- It has the following side effects
   a- Short duration of action = 4-6 Hours.
   b- Acid sensitive = Destroyed by gastric acidity = NOT effective Orally.
   c- β-Lactamase (Penicillinase) sensitive = NOT effective in β-lactamase secreting organisms e.g. Most of Staphylococcus aureus.
   d- Narrow spectrum = NOT effective against Gram -ve Bacilli e.g. Salmonella, Shigella, H. influenza, Helicobacter pylori & E. coli.
3- Dose: 1- 5 million U / 6 hours IM or IV or IV Infusion.

2- Long Acting Penicillins: (Side effects b, c & d)

1- **Procaine penicillin G** : 600'000 U IM / 12-24 hours.

2- **Fortified Procaine Penicillin G** (Diacillin, Penicillin-Proc)
= Penicillin G (100'000 U) + Procaine penicillin (300'000 U) IM / Day
→ Quick onset + Long duration.

3- **Benzathine Penicillin G** (Durapen, Lastipen, Penadur L.A., Penacid L.A.) :
1.2 - 2.4 million U IM / 1 - 4 Weeks.
- Its blood level during the first week is curative.
- Its blood level in the subsequent weeks is prophylactic.

3- Acid Resistant Penicillins: Orally (Side effects a, c & d)

1- **Phenoxymethyl penicillin** (**Penicillin V**, Ospen, Cliacil, V-pen):
2- A *natural* penicillin. Dose 250- 500 mg / 4 hours Orally.

4- β-Lactamase (Penicillinase) Resistant: (Side effects a, b & d)

1- **Methicillin** → Nephrotoxic → Obsolete
2- Used mainly to diagnose Methicillin-Resistant-Staph.-Aureus (MRSA) infection.

5- Acid & β-Lactamase Resistant Penicillins → Oxa:

Effective ORALLY in treatment of Staph. infections. BUT Weaker than penicillin G.
1- **Oxacillin**.
2- **Cloxacillin** (Prostaphlin).
3- **Dicloxacillin** (Penestaph).
4- **Flucloxacillin** (Flucillin, Fluoxil).
} 250-500 mg / 4-6 hours Orally.
5- **Nafcillin** (Unipen) 6-12 g/day IV in Severe Staph infections. Entero-Hepatic Circulation.

6- Broad-Spectrum Penicillins → ***Amino***-penicillins:

- Effective against Gram +ve & -ve organisms including Gram -ve Bacilli e.g. ***S***almonella, ***S***higella, ***H***. influenza, ***H***. pylori & ***E***. coli.
- BUT NOT effective against ***K***lebsiella, ***P***roteus & ***P***seudomonas aerugenosa.
- β-Lactamase sensitive = NOT effective in most of Staph. aureus infections.
- Acid resistant = effective orally.

1- **Ampicillin** *(Amphipen, Epicocillin, Ampicyn, Amblosin, Pentrexyl, Hicillin)* 1-2 g/day:
a- Incompletely absorbed orally & affected by food →
- Useful in enteritis. ***BUT*** - Disturb intestinal flora.
b- Short duration of action → 6 hours.

2- **Pro-Ampicillins** (Esters of Ampicillin) :
a- Pivampicillin. b- **Bacampicillin** (Penglobe). c- Talampicillin.
d- Hetacillin. e- **Epicillin** (Dexacillin).

- Prodrugs = Inactive by themselves → No effect on intestinal flora.
- They are better absorbed orally than Ampicillin.
- They are de-esterified in gut mucosa and liver → Release Ampicillin.

3- **Amoxicillin** (**Amoxycillin**, *Amoxil, E.Mox, Ibiamox, Hiconcil, Moxipen, Amoxicid):*
Similar to Ampicillin BUT:

a- Better absorbed orally & not affected by food:
- Less disturbance of flora. ***BUT*** - Less effective in enteritis.

b- Longer duration of action → 8 hours.

7- Extended Spectrum (Antipseudomonal) Penicillins:

- Broad spectrum + Effective against Pseudomonas aeruginosa & Proteus.
- They are β-Lactamase sensitive.
- Combined with Aminoglycosides (Gentamicin) → Synergism & avoid resistance.

1- Carobxy-penicillins → Platelet dysfunction → Bleeding:

a- **Carbenicillin** (Pyopen) IM & IV
b- Carbenicillin indanyl Orally
c- **Ticarcillin** (Ticarpen) IV

2- Ureido-penicillin → Stronger than carboxypenicillins → Effective in Klebsiella

a- Mezlocillin (Baypen) IV
b- **Azlocillin** (Azlocil) IV
c- **Piperacillin** (Pipril) IM & IV

8- Reversed-Spectrum Penicillins (Amidino-Penicillins):

1- Effective against Gram -ve Bacteria e.g. Salmonella & Shigella
BUT NOT Pseudomonas or Klebsiella or H. Influenza.
2- Useful in urinary tract infection & in Typhoid fever.
3- Members:
a- **Mecillinam** (Selexidine) IM & IV
b- **Pivmecillinam** (Selexid) Orally

* Pharmacokinetics of Penicillins:

1- Acid resistant Penicillins are absorbed ***orally***. Usually affected by meal, specially Dicloxacillin & Ampicillin. Better taken 1 h before or 2 hours after meals.

2- ***Distribution***:
a- All over the body.
b- Very little passage across normal BBB. Pass easily inflamed meanings.
c- Pass easily placental barrier; but NOT Teratogenic.
d- They are bound to plasma proteins.

3- Active ***Renal*** tubular excretion # Probenecid.
Readjust the dose in patients with impaired renal function.
Nafcillin is excreted mainly in bile → Enterohepatic circulation.

4- ***Metabolized*** by bacterial enzymes:
a- β-lactamase (Penicillinase) → Penicilloic acid → Inactive & Hapten → Major determinant for allergic reactions
b- Amidase → 6-Amino-penicillancic acid → Used in semi-synthetic penicillins.

* Antibacterial Activity of Penicillins:

1- Bactericidal. Mechanism of action, Selectivity & Resistance (see before).

2- Spectrum:

A) Narrow Spectrum Penicillins:

a- Gram +ve Cocci: Streptococci, Staphylococci & Pneumococci.
b- Gram -ve Cocci: Neisseria gonorrhea & N. meningitides.
c- Gram +ve Bacilli : Clostridium tetani (Tetanus), Clostridium perfringens (Gas gangrene), Corynebacterium diphtheriae (Diphtheria) & Bacillus anthracis (Anthrax)
d- Anaerobes *EXCEPT* β-lactamse secreting Bacteroides fragilis.
e- Spirochetes : Treponema pallidum (Syphilis).
f- Actinomycetes : Actinomyces israelii (Actinomycosis).

B) Broad Spectrum Penicillins:

a- The above +
b- Gram -ve Bacilli : Salmonella typhi & paratyphi, Shigella, , Haemophilus influenza, Helicobacter pylori & Escherichia coli

C) Extended Spectrum (Antipseudomonal) Penicillins:

a- The above +
b- Klebsiella pneumonia, Indole positive Proteus & Pseudomonas aeruginosa,.

NB) β-Lactamase (Penicillinase) Inhibitors:

1- Examples : Clavulanic acid, Sulbactam & Tazobactam.
2- They bind with the enzyme → Irreversible inhibition → Suicide substrate.
3- They have very weak or no anti-bacterial activity.
4- They protect penicillins from inactivation by β-lactamases secreted by some bacteria e.g. Proteus, E. coli, Pseudomonas, Staph aureus & H. influenza **(P.E.P.S.I.)**
5- Preparations :
   a- Clavulanic acid + Amoxicillin = **Co-Amoxiclav, E-Moxclav & Augmentin** Orally.
   b- Clavulanic acid + Ticarcillin = **Timentine** IV.
   c- Sulbactam + Ampicillin = **Unasyn** Oral, IM & IV.
   d- Tazobactam + Piperacillin= **Tazocin, Zosyn** IV.

* Therapeutic Uses of Penicillins:

A) Treatment of:

1- Gram +ve Cocci:
   a- Streptococcal infections e.g. Pharyngitis.
   b- Staphylococcal infections e.g. Abscess → Use β-lactamase resistant penicillins or add β-lactamase inhibitor.
   c- Pneumococcal infection e.g. Lobar pneumonia
2- Gram –ve Cocci:
   a-Meningococcal meningitis, Benzyl penicillin (G) up to 20 million U/day IV → Passes inflamed meninges.
   b- Gonorrhea.

(Cont. →)

3- Gram +ve Bacilli: Anthrax, Diphtheria, Tetanus & Gas gangrene.
4- Spirochetes: Treponema pallidum (Syphilis).
5- Actinomycosis.
6- Gram –ve Bacilli → Use Broad spectrum penicillins e.g. Ampicillin & Amoxicillin:
   a- Urinary tract infection (U.T.I.) b- Typhoid fever.
   c- H- influenza : Broad spectrum penicillin + β-lactamase inhibitor.
   d- Helicobacter pylori → Peptic ulcer: Amoxicillin 500 mg tds for 2 weeks.
7- Pseudomonas: Anti-pseudomonal penicillin + Aminoglycoside e.g. Gentamicin.

B) Prophylaxis of:

1- Streptococcal infection in Rheumatic fever: Benzathine penicillin 1.2 million U IM/ month for 5 years or up to age of 20 which is ever longer.
2- Bacterial endocarditis: In patients with rheumatic fever or prosthetic cardiac valves. Procaine penicillin 600'000 U IM 2-3 hours before dental procedures.
3- Gonorrheal neonatal ophthalmia: Benzyl penicillin eye drops.

* Adverse Effects of Penicillins:

1- ***Allergic*** Reactions: Urticaria, angioedema & Anaphylactic shock:
   a- Avoid by: - Ask for previous history. - Dermal sensitivity test.
   b- Treatment of Anaphylactic shock: Adrenaline + Cortisol + Antihistaminic.
   c- Never reuse penicillin again.
   d- Cross allergy with Cephalosporins (10%).

2- *Jarisch-Herxheimer reactions* :
   a- Only first injection in Spirochetal infections e.g. Syphilis.
   b- Treatment by cortisol. c- Continue penicillin therapy.

3- *Diarrhea* due to superinfection, specially after oral Ampicillin:
   a- Candida albicans → Monilial thrush & Diarrhea. Treat by ***Nystatin***.
   b- Antibiotic associated (Pseudomembraneous) colitis. Caused by enterotoxins produced by Staph. or Clostridium difficil. Treated by ***Oral Vancomycin*** or ***Metronidazole***.

4- *CNS irritation* (seizures) may occur if LD or intra-thecal injection of penicillin.

5- Usually we use *Na^+ or K^+* salts of penicillins. LD of penicillins → Na^+ or K^+ over load, which could be dangerous in patients with renal or cardiac problems.

6- *Benzathine* penicillin → Pain, enduration & tenderness at site of injection.

7- *Ampicillin* induces skin rash in 10% of patients & in ALL patients with infective mononucleosis, leukemia & taking allopurinol.

8- *Methicillin* → Nephritis.

9- Carboxy-penicillins e.g. *Carbenicillin* → Platelet dysfunction → Bleeding.

2- CEPHALOSPORINS

1- β-Lactam antibiotics. Derivatives of 7-Aminocephalosporanic acid.
2- Anti-bacterial activity = Penicillins → Bactericidal & ↓ cell wall synthesis.

* Classification:

All Cephalosporins are **NOT** active against MRSA, C. difficile & Enterococci (Strept. faecalis).

A) First Generation Cephalosporins:

1- Broad spectrum. Active mainly against Gram +ve organisms (Including Staph aureus) > Gram -ve bacilli BUT NOT H. influenza, Proteus or P. aeruginosa.
2- Resistant to β-Lactamase enzymes.
3- Do *Not* cross meanings. NOT effective in meningitis.
4- Preparations:

a- Oral Preparations 250-500 mg / 6-8 hours :

- **Cephalexin** (Ibilex,, Keflex, Neocef, Palitrex, Ospexin) :
- **Cephadroxil** (Ibidroxyl, Curicef, Duricef) : Long acting → 12 hours.
- **Cephradin** (Velosef, Ultracef).

b- Parenteral Preparations: IM & IV

- **Cephapirin** (Cefatrexyl)
- Cephazoline (Ancef, Kefzol) → *Long* acting & concentrates in *Bone*.
- Cephalothin (Keflin)

B) Second Generation Cephalosporins:

1- Broader spectrum. Similar to first generation But Less active against Gram +ve & MORE active against Gram -ve e.g. H. influenza (Not Pseudomonas) & Anaerobes (Not B. fragilis).
2- *More* resistant to β-Lactamase enzymes.
3- Do NOT pass BBB. EXCEPT **Cefuroxime → B.B.B.**
4- Preparations:

a- Oral Preparations:

- **Cefuroxime axetil** (Zinnat) : Long t ½ , ½ g bid. Some BBB.
- **Cefaclor** (Ceclor).
- **Loracarbef** (Lorabid). Synthetic carbacepham, identical to cefaclor.

b- Parenteral Preparations:

- **Cefuroxime** (Zinnat)
- **Cefamandole** (Mandol).
- **Cefoxitin** (Mefoxin) → Most powerful against **Anaerobes** *(Intra-abdominal, pelvic & gynecological infections)*, *But* → Hypoprothrombinemia & Disulfiram-like.
- Cefotetan. - Cefmetazole (Zefazone). - Cefonicid. - Ceforanide.

C) Third Generations Cephalosporins:

1- Broader spectrum against Gram +ve & -ve, aerobes & anaerobes.
Similar to second generation but LESS on Gram +ve & MORE on Gram -ve.
2- *More* Resistant to β-Lactamase enzymes.
3- Excellent pass *B.B.B.*
4- Members:

a- Oral Preparations:

- **Cefixime** (Suprax) 200-400 mg once/day.
- **Cefpodoxime** (Orelox) 100 mg bid.

b- Parenteral Preparations:

- **Cefotaxime** (Claforan):
Passes *BBB*, so useful in Gram –ve meningitis.
Partially de-acetylated & partially excreted unchanged in urine.
- **Ceftriaxone** (Rocephin):
Long t ½ , used Once/Day.
Concentrated in CSF (Brain) & Bone.
Excreted mainly in Bile, so allowed in renal patients without readjusting the dose.
- **Cefoperazone** (Cefobid): Especially active against P. aerugenosa.
Excreted in bile, allowed in renal patients without readjusting the dose.
Less BBB → Less effective in meningitis.
N.B.) Cefoperazone + Sulbactam (β-Lactamase Inhibitor) → *Sulperazone*.
- **Ceftazidime** (Fortum): Especially against in P. Aeruginosa. Effective in meningitis.
- Ceftizoxime (Cefizox).
- Moxalactam (Moxam).

D) Fourth Generation Cephalosporins:

1- Similar to 3rd generation *Ceftazidime, BUT* More resistant to β-lactamase enzymes.
2- Examples:
a- **Cefepime** (Maxipime): ½ - 1 g bid IV.
b- **Cefpirome** (Cefrom): 1 g bid I.V.

* Therapeutic Uses of Cephalosporins:

1- Infections resistant to penicillins (**NOT** MRSA, C. difficile & Enterococci).
2- Pseudomonal infections: Cefoperazone & Ceftazidime.
3- Anaerobic infections *(Intra-abdominal, Pelvic & Gynecological)* → *Cefoxitin.*
4- Gram -ve Meningitis: Cefotaxime & Ceftriaxone.
5- Respiratory tract infection.
6- Typhoid fever → Ceftriaxone & Cefoperazone.
7- Urinary tract infections specially Gram -ve.
8- Gonorrhea → Ceftriaxone.
9- Pre- & Post-operative → First or Second generation Cephalosporin.

* Toxicity of Cephalosporins:

1- Allergy & partial Cross-allergy with Penicillins (10%).
2- GIT upsets and Superinfections.
3- Irritant: - I.M. → Painful, so add lidocaine. - I.V. → Thrombophlebitis.
4- Nephrotoxicity specially Cephaloridine (Ceporan).
It is augmented by concurrent use of Frusemide and Gentamicin.
5- Ceftriaxone + Calcium → Insoluble salts in Bile → Biliary Sludge.
6- Cefamandole, Cefoxitin & Cefoperazone → *Methyl-Tetrazole-Thiol-Methyl = MTTM* →
a- Hypoprothrombinemia (can be prevented by Vit K 10 mg twice weekly)
b- Disulfiram like action → Alcohol intolerance.
7- Moxalactam inhibits platelet function.

* Pharmacokinetics of Cephalosporins:

1- Absorption → Some Oral & Some Parenteral.
2- Distribution → All over the body. Third generation → Pass B.B.B.
3- Fate:
a- Active Renal tubular excretion # Probenecid *(Similar to Penicillins).*
b- Cefotaxime → Partially de-acetylated & partially excreted unchanged in urine.
c- Ceftriaxone & Cefoperazone → Biliary excretion → Stool.

3- *Monobactams* → Aztreonam *(Azactam)* 1-2 g / 6-8 hours IV.

1- β-Lactam antibiotic. Binds to PBP-3 → ↓ Cell wall synthesis → Bactericidal.
2- β-Lactamase resistant.
3- Narrow spectrum → Mainly Aerobic Gram -ve bacteria including P. aeruginosa, N. gonorrhea & H. influenza. NOT effective against Gram +ve or anaerobes.
4- 100% bioavailabity after IM. Depends on Renal excretion.
5- Uses: Gram -ve infections specially is patients allergic to penicillins.
There is NO cross-allergy with penicillins.
6- Adverse Effects:
a- Colonization of Gram +ve organisms.
b- Pseudomembranous colitis: Treated by Oral Vancomycin or Metronidazole.

4- *Carbapenems* → Imipenem & Meropenem

A) **Imipenem**: ½ - 1 g / 6 hours. Readjust the dose in renal impairment.
1- β-Lactam antibiotic. Binds with PBP-2 → ↓ Cell wall synthesis → Bactericidal.
2- Very wide spectrum, Gram +ve & -ve and aerobes, & anaerobes growing or not.
3- Inactivated by renal tubular dihydropeptidase enzyme → Nephrotoxic metabolite.
NB) ***Cilastatin*** (A dihydropeptidase inhibitor). *Imipenem + Cilastatin =* ***Tienam***.
4- Used IV in serious hospital acquired (Nosocomial) infections.
5- Adverse effects :
a- Allergy and partial cross-allergy with penicillins. b-GIT disturbances. ***c- Seizures***.

B) **Meropenem** *(Meronam ½ - 1 g bid or tds I.M. or I.V.)* Similar to Imipenem ***BUT***:
a- *Not* metabolized by dihydropeptidase enzyme.
b- *Less* liable to produce seizures.

* Vancomycin (Vancocin) ½ g vials Slow I.V. Infusion

1- Inhibits early steps of Cell wall synthesis → Bactericidal.

2- Gram +ve organisms including MRSA, C. dificil & Enterococci.

3- NOT effective Orally. Used by SLOW IV Infusion.

a-Passes BBB in Meningitis.

b-Excreted in urine by passive glomerular filtration. Readjust dose in Renal patients.

3- Used:

a- IV in MRSA & Enterococcal infections.

b- IV prophylactic before dental operations in patients with prosthetic valves or joints

c- Orally in pseudomembranous colitis.

4- Adverse Effects

a- Ototoxic. b- Nephrotoxic.

c- Rapid IV infusion → Histamine release → Red man syndrome & Shock.

* Bacitracin:

1- Mixture of polypeptides.

2- ↓ Early steps of Cell wall synthesis → Bactericidal.

3- Spectrum :Gram +ve organisms → Used Topically in Staph aureus infections.

5- Adverse effect → Nephrotoxic.

* Polymixin B:

1- Basic polypeptide. Cationic detergent → ↓ Cytoplasmic MEMBRANE function → Leakage of macromolecules & electrolytes → BACTERICIDAL.

2- Affects MAINLY Gram -ve organisms

3- Used ONLY Locally:

a- Topically (Usually + Neomycin) as eye drops or skin preparations.

b- Orally (NOT absorbed) to sterilize the gut.

4- Nephrotoxic.

Macrolide Antibiotics

1- Erythromycin *(Erythrocin):* 250 - 500 mg / 6 hours.

2- Clarithromycin *(Klacid):* 250 – 500 mg 1 X 2 X 7

3- Azithromycin *(Zithromax)*: ½ g 1 X 3 or ½ g in first day then ¼ g on days 2 to 5.

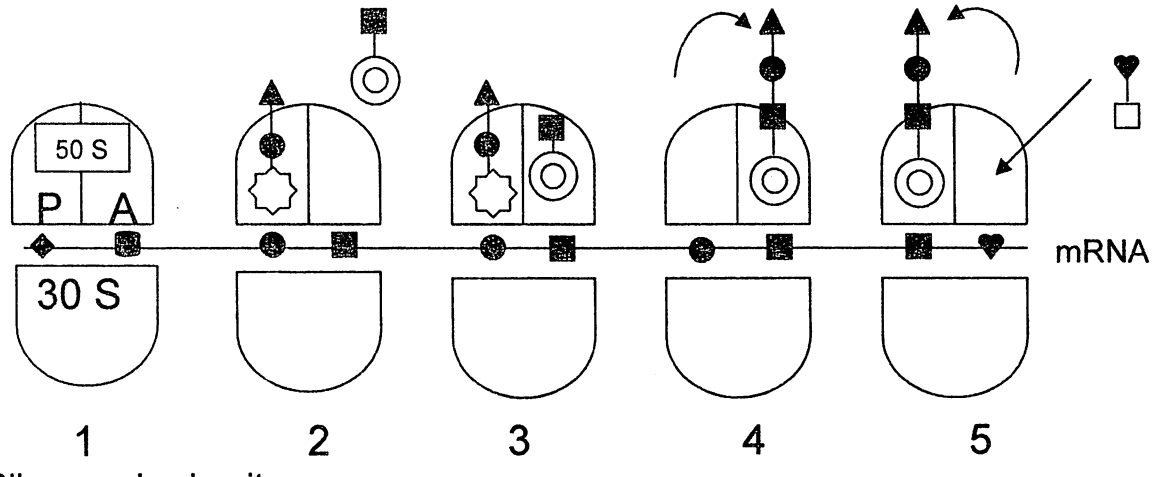
4- Roxithromycin *(Rulid)*: 150 - 300 mg od or bid an hour before meals

5- Spiramycin (Rovamycin): 200-300 mg (1.5 – 3 Mega Units) twice/day.

1- Erythromycin *(Erythrin, Erythrocin, Erythrocid)*

* Pharmacokinetics:

1- Absorbed Orally, BUT acid-sensitive. Used as enteric coated or as an Esteolate ester.
2- Distribution
   a- ALL over the body BUT NOT CSF.
   b- Concentrated in prostatic fluid.
   c- Accumulates inside macrophages & PMNL.
3- Hepatic metabolism → Excreted in bile → Enterohepatic circulation.



1- Ribosomal subunits.
2- Arrival of Amino-acyl tRNA
3- Codone / Anticodone recognition → Reading of mRNA.
4- Transamination → Release of Old tRNA.
5- Translocation from A to P site → Free A site ready for new tRNA.
6- Shift of mRNA.

* Anti-Bacterial Activity:

1- They bind irreversibly to *50 S ribosomal subunits* → *↓ Translocation* → *↓ Protein synthesis*. They share the same binding site of Lincomycin, Clindamycin & Fucidic acid *But* → Mutual antagonism.
2- Bacterio*static and cidal* according to drug's concentration.
3- *Selectivity*: Humans have different ribosomal subunits (40 S & 60 S).
4- *Resistance*:
   a- Decreased uptake by bacteria.
   b- Plasmid mediated change in 50 S ribosomal subunits.
   c- Plasmid mediated increased activity of erythromycin esterase & methylase.
5- *Spectrum*: Erythromycin has similar BUT NOT identical to penicillin G:
   a- Gram +ve cocci : Strept., staph. & pneumococci.
   b- Gram +ve bacilli : corynebacterium diphthriae.
   c- Gram -ve cocci: Gonorrhea.
   d- Some Grame -ve bacilli: Helicobacter, H. influenza, B. pertussis & Legionella.
   e- Mycoplasma pneumonia.
   f- Chlamydia.
   } Intracellular organisms
   g- Spirochetes: Treponema pallidum.

* Therapeutic Uses of Macrolides:

1- Drug of CHOICE in Bordetella pertussis.
2- Drug of CHOICE in corynebactrial infections e.g. Diphtheria.
3- Drug of CHOICE in Atypical Pneumonia caused by Mycoplasma & Legionella.
4- Drug of CHOICE in Chlamydial infection : Respiratory, Genital & ocular.
   Specially in Neonates & Pregnancy.
5- Sexually transmitted diseases (STD): Gonorrhea, Syphilis & Chlamidia.
6- Penicillin substitute in Staph., Strept.& Pneumococcal in patients allergic to penicillin.
7- In rheumatic patients taking penicillin as prophylaxis prior to dental procedures to avoid bacterial endocarditis.
8- Topically in Acne vulgaris.

* Adverse Effects of Macrolides:

1- Most common is Epigastric pain. Erythromycin > Others.
2- Cholestatic jaundice. Most probably due to estoelate ester.
3- LD of erythromycin → Reversible Ototoxicity.
4- Drug Interactions:
   a- Erythromycin & Clarithromycin (NOT Azithromycin) inhibit Cytochrome P 450
      → ↓ Metabolism of Theophylline, Carbamazepine & Warfarin → Toxic concentrations.
      ↓ Metabolism of Terfenadine & Astemizole (NOT Loratidine) → Cardiac arrhythmias.
   b- Erythromycin inhibit intestinal flora → ↓ Metabolism of Digoxin → ↑ Its Absorption.

NB) ***Azithromycin*** *(Zithromax)* & ***Clarithromycin*** *(Klacid)*:

1- Similar to Erythromycin. BUT
2- Longer duration of action.
3- Less side effects.
4- More effective especially against Gram -ve organisms e.g. H. influenza & H. pylori. & Mycoplasma.
   Clarithromycin is used to eradicate Helicobacter pylori infection in peptic ulcer

NB) Ketolides:

1- Example: ***Telithromycin*** *(Ketek, 800 mg/day for 5-10 days orally).*
2- Semisynthetic derivative of Erythromycin.
3- Not metabolized by methylase enzyme → Less bacterial resistance.
4- Similar mechanism & spectrum to Erythromycin.
5- Used mainly in respiratory tract infection e.g. Bronchitis, sinusitis & pneumonia.
6- ↓ CYP 3A4 → Many drug interactions.
7- Adverse effects: Visual disturbances, Cardiac arrhythmia, GIT disturbances, Pseudomembranous colitis & worsens myasthenia gravis.

Lincosamines

* Examples:

1- Lincomycin (Lincocin)
2- Clindamycin (Dalacin-C): 300 mg/ 6 Hours Orally.

* Pharmacokinetics:

1- Absorbed orally & Parenterally.
2- Distributed all over the body BUT NOT CSF. Concentrated in Bone & Teeth.
3- Metabolized in liver and excreted in bile → Enterohepatic cycle.

* Antibacterial Activity:

1- Similar to Erythromycin. Binds to 50 S Ribosomal Subunit → ↓ Translocation → ↓ Protein synthesis. Similar to Macrolides BUT → Mutual antagonism.
2- Similar *Spectrum* to Penicillin G & Erythromycin. More effective against Anaerobes.

* Therapeutic uses of Lincosamines:

1- Bone & Teeth infections.
2- Intra-abdominal Anaerobic infections (Add Aminoglycosides)
3- Locally in acne vulgaris.

* Adverse Effects of Lincosamines:

1- Fatal pseudomembranous colitis (C. difficile) treated by Vancomycin or Metronidazole.
2- GIT disturbances & impaired Liver function.

Fusidic Acid & Sodium Fusidate (Fusidin)

1- Steroid anti-microbial.
2- Binds to 50 S Ribosomal Subunits → ↓ Translocation → ↓ Protein synthesis.
3- Used exclusively against β-lactamase producing STAPHYLOCOCCI.
4- Readily absorbed orally. Distributed all over the body. Concentrated in Bone. Metabolised in Liver and excreted in urine.
5- Uses:
   a- Orally & IV in severe SATPHYLOCOCCAL infection including Osteomyelitis. ADD anti-staphylococcal penicillin e.g. Nafcillin to avoid resistance.
   b- Ointment and gel for STAPYLOCOCCAL skin infection & to eradicate STAPHYLOCOCCAL nasal carrier.
6- Side Effects: Mild GIT upsets.

Aminoglycosides

Obtained from Streptomyces (mycin) or Micromonospora (micin).

* Antibacterial Activity:

1- Bactericidal Antibiotics.

2- Mechanism of Action:

a- They bind to 30 S ribosomal subunit → ↓ Codone/Anticodone recognition → Misreading of mRNA.
b- **↓ Protein Synthesis** & may interfere with the cytoplasmic Membrane function.
c- Aminoglycosides concentrate inside bacteria by O_2-requiring active transport mechanism
d- Not effective against Anaerobes.
e- Chloramphenicol blocks this transport system (Antagonism).
f- More active in Alkaline media. Reducing agents eg Vit C decrease their activity.

3- **Narrow** Spectrum:
a- Effective mainly against *Gram -ve Bacilli* including Pseudomonas, Proteus & Klebsiella.
b- Also active against *some Gram +ve Cocci* e.g. β-lactamase producing Staph. Aureus & Enterococci *(Streptoccoal viridans & Faecalis → Endocarditis)*.
c- *Mycobaterium T.B.* is sensitive to Streptomycin, Kanamicin, Amikacin & Gentamicin.
d- NOT active against anaerobes.
e- They are usually combined with Penicillins. Penicillins through lysis of cell wall will facilitate entrance of Aminoglycosides and also both have complimentary spectra → Synergism.
NEVER mix Aminoglycosides (Strong Base) with Penicillin (Acidic) in the same container or infusion fluid → Inactivation.

4- **Resistance**:
a- Deletion or alteration in 30 S receptors (Chromosomal mutation).
b- Decreased active uptake into bacteria (Plasmid or Chromosomal).
c- Plasmid-induced increased metabolizing enzymes.
Amikacin & Netilmicin are Resistant to these enzymes.

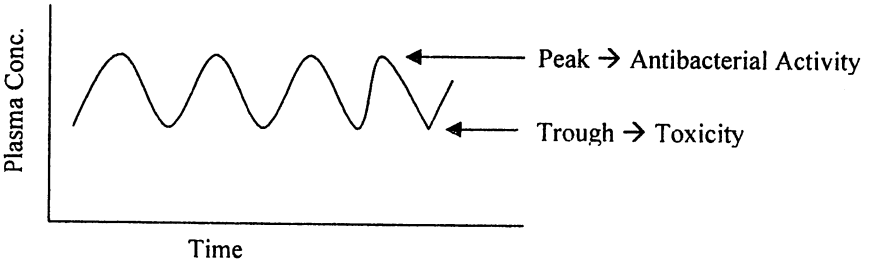
* Pharmacokinetics of Aminoglycosides:

1- They are Polycationic = Polarized = Ionized = Poor lipid solubility.
2- Poorly absorbed orally.
3- Distributed extra-cellularly. Low tissue levels.
a- Limited passage across BBB or the Eye.
b- Concentrated in renal cortex and, endolymph & perilymph of inner ear.
c- Passes placental barrier → Concentrated in fetal plasma and amniotic fluid → Fetal deafness.
4- Minimal Plasma protein binding; except streptomycin.
5- Excreted mainly unchanged in urine by Passive glomerular filtration.

** Readjust the dose in Renal Impairment:*

a- Reduce the dose BUT maintained 8 hour interval:
Adjusted dose = Normal dose / Serum Creatinine (mg/dl).

*b- **Better** maintain the dose BUT Prolong the intervals:*
Adjusted interval (hours) = Serum Creatinine (mg/dl) X 8 hours.
This is better because antibacterial activity depends on maximum concentration (Peak); while toxicity depends on trough concentration.



* Toxicity of Aminoglycosides:

1- Ototoxicity:

a- Irreversible damage of Vestibulo-auditory 8th Cranial nerve → Vertigo & Deafness
b- Toxicity increases with increased doses, duration and age, impaired renal function and concurrent use of loop diuretics, Salicylates & Chloroquine.
c- Do frequent *Audiogram*.

2- Nephrotoxicity:

a- Usually reversible.
b- Increases in patients with poor kidney function or concurrent use of Frusemide.

3- Skeletal muscle Relaxation:

a- Decrease prejunctional release of A.Ch. & decrease sensitivity of post-synaptic sites (Curare like action).
b- May cause respiratory muscle paralysis if injected into pleural or peritoneal cavity specially in Myasthenic patients. Reversed by I.V. Ca Gluconate and Anti-Ch.E. e.g. Neostigmine or Edrophonium + Artificial Respiration.

4- Allergic manifestations e.g. contact dermatitis.

5- Drug Interactions:

a- Amphotericin-B, Polymixins, Cephalosporins & Frusemide increase their Nephrotoxicity.
b- Loop diuretics, Chloroquine & Aspirin increase their Ototoxicity.
c- Aminoglycosides potentiate competitive N-M Blockers e.g. Curare.
d- Aminoglycosides + Penicillins → Synergism. BUT NEVER mixed in same container.
e- Chloramphenicol → ↓ Bacterial Uptake of Aminoglycosides.

*** Preparations & Uses:**

A) Streptomycin: 1 g / day IM.

1- Used IM + Rifampicin + Isoniazide + Pyrazinamide in TB (Mycobacterium TB).
2- Used IM + Penicillin G in Endocarditis (Srept viridans & Gram +ve enterococci).
3- Used IM + Tetracyclines in Plague (Yersinia pestis) & Tularaemia (Francisella tularenis) & Brucellosis.
4- Used Orally to sterilize the bowel.

B) Gentamicin *(Refobacin, Garamycin, Riaminol, Cidomycinl)*: 3- 5 mg/kg/day IM or IV.

1- Used in serious Gram -ve infections (Klebsiella, Proteus, Pseudomonas, Enterobacter & Serratia), and Staphylococcal & Enterococcal infections.
2- Severe infections: Pneumonia, UT, Osteomyelitis & Septicemia.
Better add Penicillins.
3- Pseudomonal infections. Add Carbenicillin or Ticarcillin.
4- Bacterial endocarditis. Add Benzyle penicillin.
5- Methicillin-resistant Staph. aureus (MRSA).
6- Topically (Cream, ointment or Solution) in burns, wounds & skin lesions.

C) Amikacin *(Amikin, Likacin)* & Netilmicin *(Netromycin)* : 15 mg/kg/day
Useful in Gentamicin-resistant infections.

D) Neomycin:

1- Used for local use MAINLY.
2- Orally as intestinal antiseptic before intestinal operations, acute intestinal infections & Hepatic coma (ADD Lactulose).
3- Orally in Hyperlipidemia → Combine with bile acids → ↓ Their Action & absorption → ↓ Absorption of cholesterol → Increases conversion of cholesterol into bile acids.
4- Topically on skin & mucous membranes.
5- Inhalation in chest infections.

E) Kanamycin: Similar Neomycin. Used mainly orally & Topically.

f) Tobramycin *(Nebcin, Tobcin, Tobracin)* : 15 mg/kg/day
Similar to Gentamicin BUT more effective against P. aeruginosa.

G) Spectinomycin *(Togamycin)* : In penicillin resistant Gonorrhea. 2 g IM ONCE.

H) Paromomycin *(Gabbroral)* : Direct Amebicide. ½ g / 6-8 hours orally.

Amphenicols

* Preparations:

1- Chloramphenicol *(Cidocetine, Miphenicol, Levocol, Memcocetine, Veracetine).*
2- Thiamphenicol *(Thiophenicol).*

* Pharmacokinetics:

1- Well absorbed Orally & Rectally.
Absorption is affected by crystal shape & size (Polymorphism).
2- Distributed all over the body and conc. in CSF, Aqueous humor, Milk & Bile.
3- Conjugated with glucuronic acid by hepatic microsomal enzymes.
Defective in premature neonates.
4- Excreted in urine & Milk (It has a bitter taste).

* Anti-Bacterial Activity of Chloramphenicol:

1- Broad spectrum, Bacteriostatic Antibiotic. Affects Gram +ve & -ve Aerobic & Anaerobic ***Bacteria*** & ***Rickettsia***. Specially active against Salmonella typhi & paratyphi, H. influenza, N. meningitidis some Anaerobic bacteroids.
2- It binds with 50 S ribosomal subunit → ↓ Transpeptidation → ↓ Protein synthesis.
In LD it affects Mammalian mitochondrial ribosomes → Bone marrow inhibition.
3- Resistance: Inactivation by Plasmid induced acetyl transferase enzyme.

* Therapeutic Uses of Chloramphenicol:

1- Typhoid & Paratyphoid fever : Start by 750 mg / 6 hours till fever subsides then 250-500 mg / 6 hours for at least 10-14 days.
2- Bacterial meningitis specially Gram -ve H. influenza (ADD Ampicillin).
3- Other bacterial infections : ENT, Respiratory, Urinary & GIT.
4- Mixed aerobic and anaerobic infections.
5- Vancomycin-resistant enterococci.
6- Rickettsial infections : Typhus & Rocky mountain spotted fever.
7- Topically in eye and ear infections.

* Adverse Effects of Chloramphenicol:

1- ***Bone Marrow Inhibition*** → Blood dyscrasias:
a- Reversible dose-dependent inhibition of Erythropoiesis due to inhibition of mitochondrial protein synthesis.
b- Fatal aplastic anemia which is irreversible, dose-independent and may be idiosyncrasy. LESS likely to occur with Thiamphenicol.
2- ***Gray Baby Syndrome*** : In premature neonates, Chloramphenicol is NOT properly metabolized → Cummulation → Toxicity → Vomiting, hypotension, hypothermia, hypotonia, shock, collapse & Gray discoloration of skin.
3- GIT upsets & Superinfection.
4- Hepatic microsomal enzyme inhibition → Potentiate Phenytoin, Theophylline, Warfarin (Anti-coagulants), Tolbutamide & Chlorpropamide (Hypoglycemics).

Tetracyclines

* Preparations & Pharmacokinetics:

A) Low to Moderate Lipid Solubility:

1- Tetracycline *(Tetracid, Micycline, Neotetryn & Hostacycline).*
2- Oxytetracycline *(Oxytetracid, Oxycycline, Oxytetrine & Terramycin).*
3- Chlortetracyclin.

} 250-500 mg / 6 h Orally

4- Demeclocycline *(Declomycin).* 150 mg/6 h or 300 mg/ 12 h Orally.

Pharmacokinetics:

1- Incompletely absorbed orally. Affected by meal.
Absorption is ↓ by : Milk, Ca^{+2}, Mg^{+2}, Fe^{+2} & Al^{+3} → Chelation of Tetracyclines.
2- Distributed all over the body. Pass BBB (CSF 20% of plasma conc.) & Placental barriers. Concentrated at sites of calcification (Bone & Teeth).
3- Moderately bound to plasma proteins.
4- Glucuronic conjugation in liver.
5- Excretion:
a- *Mainly Urinary* by Passive Glomerular filtration.
b- Bile → Intestine → Feces or reabsorbed → Enterohepatic circulation.
c- Milk.

B) HIGH Lipid Solubility:

1- Doxycycline *(Vibramycin & Doxymycin)*: 100 mg/12 h in day-1 then 100 mg/day.
2- Minocycline *(Minocin)*: Initial 200 mg then 100 mg/12 hours.

Pharmacokinetics:

1- Completely absorbed orally. NOT affected by food.
Absorption is ↓ by milk, Ca^{+2}, Mg^{+2}, Fe^{+2} & Al^{+3} → Chelation of tetracyclines.
2- Distributed all over the body.
3- Conjugated in liver.
4- Excreted:
a- Minocycline: Urine, Bile, Feces, Milk, Tears & Saliva.
b- Doxycycline:
- Excreted in feces.
- Does NOT depend on renal excretion. Allowed in renal patients without readjusting the dose.

* Anti-Bacterial Activity of Tetracyclines:

1- *Broad Spectrum Bacteriostatic* Antibiotics.
2- Concentrated in bacteria by specific transport proteins unique to bacterial cytoplasmic membrane. Attach to 30 S ribosomal subunits → ↓ Access of the amino acyl-tRNA to mRNA-Ribosomal complex → ↓ *Protein synthesis*.
3- *Spectrum*: Most Gram +ve & -ve bacteria, Mycoplasma, Spirochetes, Chlamydia, Rickettsia & Ameba.

* Therapeutic Uses of Tetracyclines:

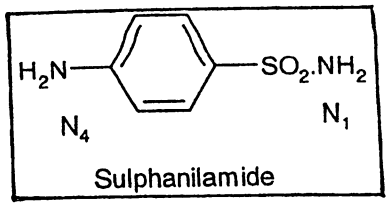
Tetracyclines are available for Oral, IM, IV, Eye Drops & Ointment

1- Most of Gram +ve & -ve Bacterial Infections (NOT TB or Typhoid):
   a- RT & ENT infections. Drug of CHOICE in Mycoplasma pneumonia.
   b- Enteritis:
      - Cholera (Doxycycline).
      - Bacillary dysentery: Shigella & Salmonella.
   c- Bacilliary Infections: Brucelosis & Tularemia *(Add Streptomycin).*
   d- Urinary tract infections.
   e- Sexually Transmitted Diseases (S.T.D., Venereal):
      - Syphilis. - Chancroid. - Gonorrhea.
      - Lymph granuloma inguibnal - Chlamydial urethritis & Cervicitis.
   f- Skin infections: Acne vulgaris.
   g- Eye infection: Topical tetracycline.
   h- Minocycline is used to eradicate Meningococcal carrier.
2- Rickettsial infections (Tetracyclines are Drugs of CHOICE): Typhus, Q-fever & Rocky mountain spotted fever.
3- Chlamydial Infection : Lymphgranuloma venerium, Psittacosis, Inclusion conjunctivitis and Trachoma.
4- Intestinal Amebiasis.
5- Demeclocycline is useful in chronic hyponatremia due to Syndrome of Inappropriate ADH secretion (SIADH)

* Side effects & Toxicity of Tetracyclines:

1- Teeth & Bone Abnormalities: If Tetracyclines are taken during pregnancy & early childhood → Chelated by Ca^{+2} & deposited in newly formed teeth & Bone →
   a- Teeth: Permanent yellow-brown discoloration & Enamel dysplasia.
   b- Bone: Deformity & inhibition of growth.
   c- Tetracyclines should be avoided during pregnancy, lactation & in children up to 8 years.
2- Teratogenecity.
3- G.I.T. irritation: Nausea, vomiting, epigastric pain & diarrhea.
4- Inhibit intestinal flora → Vit B & K deficiency & Superinfection (If in the form of Pseudomembranous colitis → Treat by Oral Vancomycin or Metronidazole).
5- Large doses especially during pregnancy → Hepatotoxicity → Jaundice.
6- Nephrotoxicity especially if they used after their expiry date → Fanconi syndrome → Azoturia, glucosuria, polyuria, polydepsia, acidosis & vomiting.
7- Hypersensitivity.
8- Photosensitivity.
9- Minocycline → CNS → Vestibular disturbances → Vertigo. Sometimes → Benign increase in intracranial pressure → Pseudo-tumor cerebri.
10- Demeclocycline → Anti-ADH → Diabetes insipidus like syndrome.

Sulfonamides



Sulphanilamide

- Synthetic chemotherapeutic agents.
- Derivatives of Para-amino-benzene sulfonamide = Sulfanilamide.
- Obtained by substitution in Amido (N_1) or Amino (N_4) groups.
- The presence of Free Amino Group (N_4) is essential for antimicrobial activity

* *Classification of Sulfonamides*:

A) Short Acting (Rapidly absorbed & Rapidly excreted):

1- Sulphadiazine: → Penetrates readily BBB → Useful in Meningococcal meningitis.
2- Sulphamerazine. } Triple sulfa → ↓ Dose of each → ↓ Crystaluria.
3- Sulphamethazine. }
4- Sulphisoxazole. } Concentrated in urine,
5- Sulphasomidine. } Soluble even in acid urine,
6- Sulphamethizole. } Useful in UT infection.

B) Intermediate Acting (Rapidly absorbed & Intermediate $t_{1/2}$ = 11 hours):

- Sulphamethoxazole (SMX + Trimethoprim (TMP) → Co-Trimoxazole → Antibacterial).

C) Long Acting (Rapidly absorbed & Slowly Excreted):

1- Sulphadimethoxine.
2- Sulphadoxine (Sulphadoxine + Pyrimethamine → Fansidar → Antimalarial).

D) Poorly Absorbed:

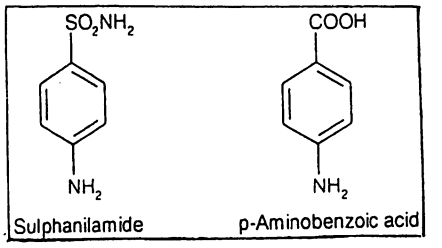
1- Sulphaguanidine. }
2- Phthalylsulphathiazole (Sulphathalidine). } Useful in bacillary dysentery.
3- Succinylsulphathiazole (Sulphasuccidine). }
4- Sulphasalazine (Salazopyrine): Useful in Ulcerative colitis.

E) Sulphonamides for Topical Use:

1- Sulphacetamide: Eye infections (Eye drops 10-30% & Ointment 6%).
2- Silver Sulphadiazine: Skin cream.
3- Mafenide (Marfanil): Skin cream & powder.

* Pharmacokinetics:

1- Short & Long acting sulfa are well absorbed orally.
2- Distributed All over the body & pass BBB and placental barriers.
3- Bound to plasma proteins. Displace bilirubin → Kernictrus in neonates.
4- Acetylated in liver → Acetylated sulfa → Inactive & Insoluble in acid urine.
5- Excreted & concentrated in urine (10-20 times > plasma).
   a- May produce Crystaluria → Prevented by plenty fluid intake & Alkalinization of urine.
   b- Readjust the dose in renal impairment.
   c- Also Excreted in milk.
6- Poorly absorbed sulfa are excreted in stool.



* Anti-Bacterial Activity of Sulfonamides:

1- ***Bacteriostatic***.

Dihydropteroate synthetase (DHPS) — Dihydrofolate Reductase (DHFR)

PABA ----------→ Folic Acid ----------→ THFA.

Sulfonamides — # Trimethoprim.

2- ***Compete with PABA*** → ↓ Dihydropteroate synthetase (DHPS) → ↓ Folic acid synthesis. Folic acid is essential for synthesis of bacterial purines & DNA.
Mammalian cells can utilize preformed folic acid.
3- ***Spectrum***:
   a- Gram +ve & -ve bacteria (NOT Pseudomonas or Proteus).
   Now many strains (Staph, Strept, Pneumo, Meningo & Gonococci) → Resistant
   b- Chlamydia trachomatis.
   c- Nocardia (Actinomycete).
   d- Some protozoa (Pneumocystis carnii).
   e- ***Not*** active against → Rickettsia, Spirochetes or viruses.
4- ***Resistance***: Through transmissible Plasmid :
   a- Overproduction of PABA.
   b- Decreased sensitivity of DHPS to sulfa BUT NOT to PABA.
   c- Utilization of preformed folic acid.
5- ***Antagonists*** (Except Mafenide): a- PABA b- Pus c- Procaine.
6- ***Synergists***: Inhibitors of DHFR e.g. Trimethoprim → Sequential block.

* Therapeutic Uses of Sulfa:

1- Meningococcal meningitis:
   a- Treatment: ***Sulfadiazine*** ½ -1 g IV then 1 g/4 hours Orally.
   b- Prophylaxis: ***Sulfadiazine*** 1 g / 12 hours Orally for 3 days (1 X 2 X 3).
2- Urinary tract infection. Especially first, previously untreated, acute attack in females.
   Sulfisoxazole 1 g single oral dose.
3- Bacillary dysentery: Poorly absorbed sulfa → Sulfa-***guanidine, thalidine*** & ***succidine***.
4- Ulcerative colitis: ***Sulfasalazine***.
5- Conjunctivitis: ***Sulfacetamide***.
6- Skin burn, wounds, leg ulcers & bed sores: ***Mafenide & Sliver Sulfadiazine***.
7- Respiratory tract infection: Sinusitis, otitis media, bronchitis & pneumonitis.
   Sulfisoxazole + Erythromycin (Pediazole) in acute otitis media in children.
8- Prophylaxis against Streptococcal infection (Sulfadiazine 1 g/day Orally).
9- Chlamydial infection, genital tract, eye & respiratory.
10- Nocardiasis → Drug of Choice → Sulfisoxazole or Sulfadiazine 6-8 g/day

* Adverse Effects of Sulfonamides:

1- **A***llergy (Hypersensitivity)*:
   a- Manifestations: Fever, Photosensitivity & Stevens-Johnson syndrome.
   b- Cross-Allergy with other Sulfonamides e.g. Diuretics (Thiazides, Frusemide, Bumetanide & Carbonic anhydrase inhibitors), Diazoxide & Sulfonylureas.

2- **B***lood dyscrasias*:
   a- Hemolysis in patients with G6PD deficiency.
   b- Bone marrow inhibition.

3- **C***rystaluria*: Avoided by, plenty fluid intake, alkalinization of urine & use of sulfonamide mixtures e.g. Triple Sulfa.

4- **D***iarrhea* → GIT disturbances & Superinfection.

5- ***D***isplace bilirubin → Kernictrus. Avoid during pregnancy & lactation.

6- **D***rug Interactions*:
   a- Displace Warfarin & Tolbutamide → Initial increase in their activity.
   b- Methenamine *(Urinary antiseptic)* → Releases Formaldehyde → Inactivates Sulfa.

7- Nephrotoxicity & Hepatotoxicity.

Trimethoprim (TMP, Triprim)

* Anti-Bacterial Activity:

1- **Mechanism**: Inhibits DHFR → ↓ conversion of DHFA into THFA (Folinic Acid).
2- Bacterial DHFR is 50'000 time more sensitive to TMP than the mammalian one.
3- **Spectrum**: Similar to sulfa but 20-50 times more potent.
4- **Resistance**: Change in the sensitivity of the enzyme.

* Pharmacokinetics:

1- Similar to that of Sulfamethoxazole *(t ½ = 11 hours).*
2- More lipid soluble → Large volume of distribution.
3- Weak Base (pKa 7.2) → *Trapped in acidic prostatic & vaginal fluids* (pH 6.4).

* Therapeutic Uses: TMP 100 mg bid orally

1- Prophylaxis & treatment of acute Urinary tract infections & Prostatitis.
2- Respiratory tract infections.

* Adverse Effect:

Megaloplastic anemia. Prevented and treated by Folinic acid 6-8 mg/day.

NB) Trimetrexate about 1500 times stronger than TMP.

Co-Trimoxazole

"Septazole, Chemotrim, Cotril, Sutrim, Septrin"

- Trimethoprim (TMP, 80 mg) + Sulfamethoxazole (SMX, 400 mg) = 1 : 5
  {Similar Compounds TMP + Sulfamoxol (Entrim, Supristol) &TMP + Sulfametrol (Lidaprim)}
- Both have similar kinetics → t ½ = 11 hours.
- TMP being more lipid soluble → Larger volume of distribution.
  Plasma ratio of TMP : Sulfa = 1 : 20 which is optimum for antimicrobial activity.

* Anti-Bacterial Activity:

1- They produce Sequential Block in the synthesis of Folinic acid & DNA → Synergism.
2- More potent, wider spectrum & less bacterial resistance than each drug alone.

* Therapeutic Uses: 2 tablets / 12 hours

1- Respiratory tract infection.
2- Urinary tract infection (UTI).
3- Protatitis.
4- Gonococcal infection (Urethral & Oropharyngeal).
4- Shigella & Salmonella enteritis.
5- Systemic salmonella (Typhoid fever & Carrier).
6- Prevention & treatment of Toxoplasmosis.
7- Prevention & treatment of Nocardiosis. Drug of CHOICE.
8- Prevention & treatment of Pneumocystis carnii in AIDS. Used by IV Infusion.

* Adverse Effects: = Both Sulfa + TMP → Megaloplastic anemia + ABCDDD

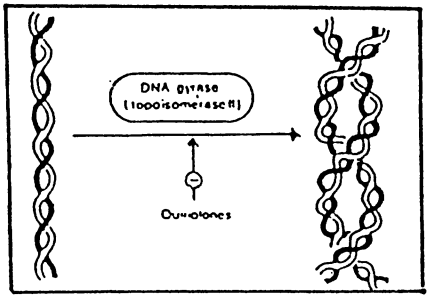
NB) Other Combinations:

1- Sulfisoxazole + Erythromycin → *Pediazole* in Acute otitis media in children
2- T.M.P. + Erthromycin → *Erythroprim* or *Primomycin* → U.R.T.I.
3- Sulfadoxine + Pyrimethamine → *Fansidar* in Chloroquine resistant Plasmodium faliciparum.
4- Sulfadiazine 6-8 g + Pyrimethamine 50 mg → Toxoplasmosis & Leishmaniasis.

Quinolones & Fluoroquinolones

* Anti-Bacterial Activity:

1- They enter the bacteria by passive diffusion through the porins → ↓ Bacterial DNA gyrase (Topoisomerase II) enzyme → ↓ Rejoining step → ↓ DNA Replication → BACTERICIDAL.
Mammalian DNA gyrase is NOT sensitive to them.



2- *Spectrum*: Fluoroquinolones 60 times more potent than Quinolones.

a- Active MAINLY against Gram -ve organisms (Pseudomonas, H. influenza, N. gonorrhea)

b- Less active against Gram +ve organisms (NOT Pneumococci or Enterococci).

c- Mycobacteria, including TB, *NOT* M. avium.

d- Mycoplasma.

e- Chlamydia.

f- NOT against Spirochetes & Anaerobes.

3- *Resistance*:

a- Chromosomal mutations in the gyrase enzyme e.g. MRSA & Pseudomonas.

b- NO cross-resistance with other anti-microbial drugs.

* Pharmacokinetics:

1- *Absorbed* orally & Injection.
Absorption is ↓ by Sucralfate, Antacids containing Mg^{+2} & Al^{+3} and food supplements containing Fe^{+2} & Zn^{+2}.

2- *Distributed* All-over the body tissues & fluids:
- a- Low CSF levels, EXCEPT Ofloxacin & Pefloxacin = 90% of plasma level.
- b- Concentrated in *prostatic tissue* & NOT fluid.
- c- *Intracellularly* into Macrophages & PMNL → Useful against intracellular organisms such as TB, Chlamydia, Mycoplasma & Brucella.

3- *Metabolized* in liver EXCEPT Ofloxacin & Lomefloxacin.

4- *Excretion*:
- a- Urine: Can by # by Probenecid → Similar to penicillins.
  Can cause Crystaluria → Similar to Sufonamides.
  Readjust the dose in renal impairment.
- b- Biliary.

* Adverse Effects:

1- Allergy & Photosensitivity, use sun-screens & sun-blocks.

2- CNS: Headache, dizziness & confusion → Avoid driving.
Seizures specially if used with NSAID → Avoid in Epileptics.

3- GIT upsets.

4- ***Chondrolytic*** → Reversible Arthropathy → Avoid in pregnancy, lactation and in children up to age of 18 years.

5- Rupture of tendons (Achilles tendon) in elderly taking glucocorticoids.

6- Nephrotoxic & Crystaluria.

7- Drug Interactions of Fluoroquinolones:
- a- Ciprofloxacin, Ofloxacin & Enoxacin → Enzyme inhibitors → ↓ Metabolism of Theophylline, Warfarin & Sulfonylureas.
- b- Cimetidine → ↓ metabolism of Fluoroquinolones.
- c- Sucralfate, Antacids (Mg^{+2} & Al^{+3}) & Food supplements (Fe^{+2} & Zn^{+2}) → ↓ absorption of Fluoroquinolones.
- d- Fluoroquinolones + NSAID → Seizures.

* Members & Uses of Quinolones & Fluoroquinolones:

A) First Generation Quinolones:

1- *Examples:* Nalidixic acid *(Nalidram, Negram)* & Oxolinic Acid *(Urotrate)*
2- Useful in prevention and treatment of Urinary Tract Infections (UTI), NOT Pseudomonal. *Not* useful in systemic infections.

B) Second Generation Quinolones:

1- *Examples*: Pipemidic Acid *(Pipram)* & Cinoxacin.
2- Similar to First Generation Nalidixic acid.

C) Third Generation *Fluoro*-quinolones:

1- More potent 60 times > Quinolones.
2- Useful in systemic infections.

1- Norfloxacin *(Neofloxacin, Noracin, Noroxin, Spectrama)*: Dose 400 mg bid Orally. In Acute & Recurrent UTI (including P. aeruginosa), Prostatitis and Typhoid.

2- Lomefloxacin *(Lomeflox)*:
In UTI & Bronchitis caused by H. influenza & Moraxella *(NOT Pseudomonas)*.

3- Ofloxacin *(Kiroll, Oflicin, Tarivid)*: 200 - 300 mg twice daily.
UTI, Prostatitis, Sexually transmitted diseases (S.T.D.) e.g. Gonorrhea & Chlamydia (***BUT NOT*** Syphilis), and Lower Respiratory tact infections (H. influenza & Mycoplasma).

4- Pefloxacin *(Peflacin)*: 400 mg bid PO & IV infusion (5% glucose & NOT saline).

5- Ciprofloxacin *(Ciprinol, Mifoxin)*:
1- Most potent.
2- Dose: Oral 250-750 mg bid & I.V. 200 mg bid.
Half the dose when GFR < 20 ml/min
3- Uses:
a- R.T.I.:
- Effective mainly in *atypical pneumonia* e.g. Mycoplasma.
- Effective in Mycobacterial infections e.g. *Multi-drug resistant T.B*.
- *NOT* very effective in pneumonia & sinusitis caused by Pneumococci.

b- G.I.T. Infections:
- Diarrhea eg Traveller's diarrhea caused by Shigella, Salmonella, E. coli & Helicobacter.
- Typhoid fever. - Intra-abdominal infections.

c- U.T.I., Prostatitis & Sexually transmitted diseases *(S.T.D.)* e.g. Gonorrhea, Chlamydia *But Not* Syphilis.
d- Soft tissue, Bone and Joint infections.
e- Septicemia.
f- ***NOT*** active against MRSA, Pneumo-, Enterococci, Spirochetes & Anaerobes.

6- New Fluoroquinolones:
a- **Levofloxacin** *(Tavanic)* & Sprafloxacin → Wider spectrum + Gram +ve Streptococci.
b- Trovafloxacin → Wider spectrum + Enterococci.
c- Cinfloxacin → Wider spectrum + Anaerobes

Chemotherapy of Some Bacterial Infections

I- Treatment of Rheumatic Fever:

A) Treatment of Acute Attack: 10 days course of:

1- **Procaine penicillin G** 600'000 U IM o.d.
2- **Fortified procaine penicillin G** (Procaine penicillin G 300'000 U + Benzyl penicillin 100'000 U) IM od.
3- Patients allergic to penicillins → **Erythromycin** 250 mg/6 hours PO for 10 days.

B) Chemoprophylaxis:

1- Streptococcal Infection:

1- **Duration**:
   a- 5 years after the last attack or till age of 20, which is ever longer.
   b- If > 2 attacks or rheumatic carditis → Life long treatment.
2- **Penicillins**:
   a- Benzathine penicillin G 1.2 million U IM / 4 weeks.
   b- Phenoxymethyl penicillin (penicillin V) 250 mg PO bid.
3- **If Allergic to Penicillins**:
   a- Erythromycin 250 mg PO bid.
   b- Sulfadiazine 1 g PO bid.
   c- Co-Trimoxazole (SMX 400 mg + TMP 80 mg) 2 tablets bid PO.

2- Bacterial Endocarditis:

1- **Procaine penicillin** G 600'000 U IM 2-3 hours before tooth extraction.
2- **Amoxicillin** 3 g PO 1 hour before tooth extraction.
3- **Erythromycin** 1 g PO 2 hrs before extraction then ½ g PO / 6 hrs for 2 days.

II- Treatment of Typhoid Fever:

A) Acute Attack:

1- First Choice Drugs:

1- **Co-Trimoxazole** 4 tablets PO bid for 2 weeks.
2- **Ceftriaxone or Cefoperazone** 3-4 g / day IV.
3- **Ciprofloxacin** 750 mg PO bid for 2 weeks.

2- Second Choice Drugs *(Frequent resistance)*:

- **Ampicillin or Amoxicillin** 1 g / 6 hours PO for 2 weeks.

3- Third Choice Drugs *(More frequent resistance and toxicity)*:

- **Chloramphenicol** 50 mg/kg/day (750 mg/6 hours) till fever subsides, then 30 mg/kg/day (250-500 mg/6 hours) for 2 weeks.

B) Carrier Stage:

1- **Ampicillin or Amoxycillin + Probenecid** for 3 months.
2- **Co-Trimoxazole + Rifampicin** for 6 months.
3- Cholecystectomy may be required.

III- Treatment of Gonorrhea:

1- **Procaine penicillin G** 4.8 million U IM + 1 g **Probenecid** PO for 2 days.
In cases of prostatitis or salpingitis → Treatment for 1-2 weeks.
2- **Ampicillin** (3.5 g) or **Amoxycillin** (3 g) + 1 g **Probenecid** single oral dose.
3- **If Allergic To Penicillins:**
a- **Cefoxitin** 2 g IM + **Probenecid** 1 g PO.
b- **Ceftriaxone** 250 mg IM.
c- **Spectinomycin** 2 g IM.
d- **Doxycycline** 100 PO bid for 7 days.
4- *Prophylaxis*: **Doxycycline** or **Minocycline** 200 mg PO soon after exposure.

IV- Treatment of Syphilis:

1- Primary & Secondary:
1- **Procaine penicillin G** 2.4 million U IM + **Probenecid** 1 g PO for 10 days.
2- **Benzathine penicillin G** 2.4 million U IM / week for 3 weeks.

2- Tertiary Syphilis: **Procaine penicillin G + Probenecid** for 3 weeks.

3- Patients Allergic to Penicillins:
1- **Erythromycin** 500 mg PO / 6 hours for 15 days.
2- **Tetracyclines** 500 mg PO / 6 hours for 15 days.

4- Prophylaxis:
- **Benzathine penicillin G** 2.4 million U IM once.

V- Chemotherapy of Urinary Tract Infection (UTI)

*** General Measures;**

A) Culture Sensitivity test.

B) Alteration of Urinary pH:

1- To *Increase* efficacy of Anti-Microbials:
a- Acid urine *(pH < 5.5 by Ammonium chloride, Ascorbic acid, Sodium acid phosphate, Methionine & Mandelic acid)* → ↑ Activity of Penicillins, Tetracyclines, Methenamine & Nitrofurantoin.
b- Alkaline urine *(By Na or K Acetate, Bicarbonate, Citrate & Lactate)* → ↑ Activity of Sulfa, Streptomycin, Gentamicin & Erythromycin.
2- To ↓ *Growth* of some organisms: Alkaline urine → ↓ growth of E. coli.
3- Alkalinization of urine → *Relieves dysuria*.

* Drug Therapy of UTI:

A) Antibiotics:

1- **Penicillins**:
   a- If Gram –ve Bacilli → Broad spectrum Penicillins e.g. Ampicillin & Amoxicillin.
   b- If Pseudomonas → Extended spectrum Penicillin e.g. Carbenicillin + Aminoglycoside e.g. Gentamicin + β-Lactamase Inhibitor.
2- 3rd Generation **Cephalosporins** e.g. Ceftriaxone.
3- **Aminoglycosides**.
4- **Chloramphenicol**.
5- **Tetracyclines**.
6- Antibiotic **Combinations**.

B) Chemotherapeutics:

a- **Sulfonamides** e.g. Sulfisoxazole.
b- **Co-Trimoxazole**.
c- **Fluoroquinolones** e.g. Norfloxacin, Ofloxacin & Ciprofloxacin.

C) Urinary Antiseptics:

- They disinfect the *Urine* with negligible effect on kidney tissue or other organs or fluids.
- They include: Nitrofurantoin, Nalidixic acid, Methenamine & Mandelic acid.

1- Nitrofurantoin:

1- Synthetic bactericidal against E. coli & Proteus infections.
2- Acidification of urine ↑ its activity.
3- Adverse effects:
   a- Peripheral neuritis.
   b- Idiosyncrasy → Hemolysis in patients with Favism.

2- Nalidixic Acid:

1- Quinolone → ↓ DNA Gyrase enzyme → Bactericidal against E. coli & Proteus.
2- Not affected by pH changes in urine.

3- Methenamine:

1- In acid urine it releases *Formaldehyde*.
2- Used with acidifying agent e.g. Mandelic acid.
3- Inactivates sulfonamides.

VI- Chemotherapy of Tuberculosis

* Anti-Tubercular Drugs:

A) First Line Drugs → High efficacy with tolerable adverse effects.

1- **Rifampicin**: 600 mg / day PO

2- **Isoniazid**: 300 mg / day PO

3- **Pyrazinamide**: 30 mg / kg / day PO
   a- Treats mycobacterium inside Macrophages → Prevent relapse of T.B.
   b- Adverse effects → Allergy + GIT + Hepatotoxic + Hyperuricemia.

4- **Ethambutol**: 15 mg/kg/day PO → Allergy + GIT + Optic neuritis + Hyperuricemia.

5- **Streptomycin**: 1 g I.M. / 2-3 Days → Ototoxic, Nephrotoxic & N-M block.

B) Second Line Drugs:

- Less effective & More toxic.
- Used to substitute first line drugs if they fail (Resistance) or contraindicated e.g. Allergy.

1- **Para-Amino-Salicylic Acid (PASA)**: 8-12 g/day PO
a- Compete with PABA.
b- Adverse effects → GIT upset, Hepatotoxic, Nephrotoxic & ↓ Thyroid function.

2- **Ethionamide**: ½ - 1 g / day PO
a- Effective in Mycobacterium T.B. & Leprosy.
b- Adverse Effects → Allergy + GIT + Hepatotoxic.

3- **Cycloserine**: 15 – 20 mg / kg / day PO
   a- ↓ Early steps of cell wall synthesis.
   b- Adverse effects → Allergy + GIT + CNS → Psychosis.

4- **Amikacin & Kanamycin** → Aminoglycosides → Ototoxic + Nephrotoxic + N-M block.

5- **Viomycin & Capreomycin** → Polypeptides → Ototoxic + Nephrotoxic.

* Therapeutic Regimens of T.B.

1- **D.O.T.S.** (Direct Observed Therapy Short Course):
a- Drugs are taken under direct supervision in special clinics.
b- Useful to insure patient compliance.

2- **Choice** of drugs depends on the sensitivity of the prevailing T.B. strain.

3- Use drug **Combinations**:
a- ↑ Activity. b- ↓ Toxicity. c- ↓ Resistance.

4- **Dosage Schedules**:

a- **Start** by → Rifampicin + Isoniazid + Pyrazinamide for **2** months **then** followed by → Rifampicin + Isoniazid for the next **4** months.

b- **Start** by → Rifampicin + Isoniazid + Pyrazinamide + Ethambutol or Streptomycin for **2** months **then** followed by → Rifampicin + Isoniazid for the next **4** months.

c- In *multiple-drug resistant* T.B. → Add **Ciprofloxacin** to therapy.

5- **Chemoprophylaxis** → Isoniazid.

1- Rifampicin *(Rifampin, Rifadin, Rimactane):*

* *Kinetics of Rifampicin:*

1- Well absorbed orally. Affected by food → Taken 30 minutes before meal.
2- Distributed All over the body → Extra & Intra-cellularly → Macrophages.
3- Partially de-acetylated in liver.
4- Excretion:
   a- Bile → Entero-hepatic circulation.
   b- **Urine**, tears, saliva, sweat, sputum → Orange-red discoloration.

* Anti-Bacterial Activity of Rifampicin:

1- Bacteri**cidal**.
2- ↓ *DNA-dependent RNA polymerase* enzyme → ↓ Synthesis of RNA.
3- **Spectrum**: Mycobacterium T.B. & Leprosy, Some Gram +ve & -ve Bacteria, Chlamydia & pox viruses.

* Therapeutic Uses of Rifampicin:

1- First line drug in **T.B.** + Isoniazid.
2- **Leprosy**.
3- Drug of **choice** in prophylaxis of Meningococcal meningitis → 600 mg / day PO for 4 days.
4- Resistant bacterial infections e.g. Staph.

* Adverse Effects & Drug Interactions of Rifampicin:

1- *Orange-red discoloration* of secretions e.g. Tears, saliva, sweat, sputum & urine.
2- Allergy → Flu–like syndrome.
3- G.I.T. upset.
4- CNS → Headache, Confusion & Ataxia.
5- *Hepatic Microsomal Enzyme Inducer* → ↑ Metabolism of Oral anti-coagulants, hypoglycemics, contraceptives, corticosteroids, digitalis & Methadone → Withdrawal manifestations.

2- Isoniazid *(Iso-nicotinic Acid Hydrazid = I.N.H.):*

* Kinetics:

1- Well absorbed orally.
2- Distributed All over the body → Extra- & Intra-cellularly → Macrophages, C.S.F., C.N.S. & Caseous material.
3- Acetylated in liver → Idiosyncrasy → Slow & Rapid acetylators.
PASA → ↓ Metabolism of I.N.H. → ↑ Its plasma level.
4- Excreted in urine.

* Anti-Bacterial Activity of I.N.H.:

1- Tuberculo- Static & Cidal.
2- ↓ Mycolic acid synthesis → ↓ Synthesis of Cell Wall.

* Adverse Effects of I.N.H.:

1- *Idiosyncrasy*:
a- *Slow* Acetylators → ↑ I.N.H. # Pyridoxine (Vit B-6) → Peripheral neuritis. Prevented by Pyridoxine (Vit B-6) 10 – 50 mg day PO.
b- *Rapid* Acetylators → ↑ Acetyl-Isoniazid → Hepatotoxicity.
c- *Hemolysis* in patients with Favism
2- *Drug Interactions*:
a- Isoniazid → Enzyme Inhibitor → ↓ Metabolism of Phenytoin → ↑ Its plasma level.
b- Rifampicin → Enzyme Inducer → ↑ Acetylation of I.N.H. → ↑ Hepatotoxicity.

VI- Chemotherapy of Leprosy

1- Dapsone:
a- Sulfone → Compete with PABA → Bacterio-static.
b- Adverse effect → Sulfone syndrome → Exfoliative dermatitis, fever, hepatitis, lymphadenopathy, Met-Hb & Hemolytic anemia.

2- Clofazimine.
3- Thiacetazone.
4- Rifampicin.
5- Ethionamide.

6- *Treatment Regimen:* Drug Combination Orally for at least 2 years.
Dapsone 100 mg / day + Clofazimine 100 mg / day + Rifampicin 600 mg / month.

Antifungal Agents

A) Antifungal Antibiotics:

1) Polyene Macrolide Antibiotics:

1- **Fungistatic** antibiotics. They combine with Ergosterol of fungal *cell membrane* → Detergent-like action = Formation of pores → Loss of cellular macromolecules & ions.

2- **Examples:**

a- **Nystatin** *(Mycostatin)*: Treatment of Local Monilial (Candida albicans) infections
- i- GIT infection : 0.5-1.5 million U tds Orally (not absorbed).
- ii- Topically : Mouth (thrush), skin & vulva.

b- **Amphotericin B** *(Fungizone)*: IV, Drug of CHOICE for systemic fungal infections.

2- Griseofulvin:

a- Fungistatic antibiotic. It inhibits nucleic acid synthesis.
b- Orally in superficial mycosis (dermatophytes) e.g. ringworm of skin, hair & nail & athlete's foot. *NOT Effective against Candida albicans or Systemic mycosis.*
c- Hepatic microsomal *enzyme inducer* → ↑ Metabolism of oral anticoagulants.

B) Antifungal Antimetabolites:

* Flucytosine:

1- Deaminated inside susceptible fungi → 5-Fluorouracil → Antimetabolite → ↓ DNA synthesis.
2- Used orally + IV Amphotericin in Candida & Fungal infections.

C) Antifungal Azoles:

1- Fungicidal. They combine with fatty acids of fungal *cell membrane* → ↓ Synthesis of ergosterols.

2- Examples:

1- **Ketoconazole** *(Nizoral)*:
- a- Topically as 2% cream or lotion in local fungal infections and dandruff.
- b- Orally 400 mg / day for systemic & muco-cutaneous mycosis.
- c- ↓ Adrenal & gonadal (androgen) hormone synthesis → Gynecomastia, loss of libido and azospermia in males.

2- **Fluconazole** *(Diflucan)*:
- a- Similar to Ketoconazole, but lacks its endocrine side effects.
- b- Orally for oro-pharyngeal & vaginal candidiasis & various Tinea infections.

3- **Itraconazole** *(Sporanox)*: Similar to Fluconazole.

4- **Clotrimazole** *(Candistan, Canesten, Dermatin & Locasten)*:
5- **Miconazole** *(Daktarin, Miconaz)*:

} Used Topically for local fungal infection

D) **Terbinafine** *(Lamisil)*:

1- ↓ Squalene epoxidase → ↓ Synthesis of Ergoterol from Squalene → ↑ Squalene → Toxic to fungus.
2- Lipophilic → Absorbed orally & Penetrates skin & mucous membranes.
3- High affinity for keratinous tissue → Used Orally & Topically in Nail fungal infection.

Antiviral Agents

A) Inhibition of Attachment to or Penetration of Host Cells:

1- **Gamma Globulin** → ↓ Penetration: IM to prevent Measles or Infective hepatitis.

2- **Amantadine** *(Symmetrel)* & **Rimantadin**: Orally for prophylaxis of Influenza A & Antiparkinsonian. Under trial in treatment of *Hepatitis C virus*.

B) Inhibition of Nucleic Acid Synthesis:

1- **Idoxuridine (IDU)**: Thymidine analogue. Topically in Herpes simplex e.g. Keratitis.
2- **Vidarabin**: Prodrug → Phosphorylated by cellular kinase → Active Triphosphate → ↓ Viral DNA polymerase. Topically & IV in Herpes simplex.

3- **Acyclover** *(Zovirax)*: Prodrug → Activated by viral infected cells (not normal cells) → Triphosphate → Deoxyguanosine analogue → ↓ Viral DNA polymerase. Oral, parenteral & topical in herpes simplex and varicella-zoster.

4- **Gancyclovir** *(Cytovene)*: Similar to Acyclover. Used IV in life- or sight-threatening cytomegalovirus in immunocompromised patients e.g. HIV (AIDS).

5- **Foscarnet (Phosphonoformate)**: Active → ↓ DNA polymerase. IV infusion for cytomegalovirus retinitis in patients with HIV (AIDS).

6- **Ribavirin** *(Virazole)*: Purine nucleoside analogue → ↓ DNA & RNA viruses → Broad spectrum antiviral. Used *with Interferons in Hepatitis C virus* & by inhalation in viral respiratory infections.

7- **Zidovudine (Azidothymidine, AZT)**: Prodrug → Phosphorylated → ↓ Viral RNA-dependent DNA polymerase (Reverse Transcriptase). Orally for AIDS. May cause granulocytopenia & anemia.

N.B.) **Other** Reverse Transcriptase Inhibitors in Treatment of AIDS → **Didanosine, Stanosine, Zalcitabine & Lamivudine**.

C) Protease Enzyme Inhibitors:

1- ↓ Protease enzyme → ↓ Production of functional viral proteins & enzymes → ↓ Virus maturation.
2- Useful in AIDS. Used with ReverseTranscriptase inhibitors → Synergism.
3- Rapidly metabolized by CYP 450. *Grapefruit* ↓ their metabolism → Potentiation.
4- *Examples* → **Indinavir, Ritonavir, Saquinavir & Nelfinavir.**

D) Inhibition of Late Protein Synthesis:

- **Methisazone** *(Marboran)* : Orally for prophylaxis of small pox.

E) Inhibition of Assembly or Release of Viral particles:

- **Rifampicin** : For pox viruses.

F) Immuno-modulators:

- **Human Interferons**:

1- Proteins produced by viral-infected cells e.g. leucocytes & fibroplasts.
2- Viral non-specific.
3- Alter host cell ribosomes → New mRNA → Enzymes ↓ translation of viral mRNA into viral proteins.
4- Interferon α-2a & α-2b SC or IM for chronic active hepatitis (B & C) & herpes zoster.
5- Adverse effects of Interferons:
   a- Influenzá-like syndrome → Fever, headache, myalgia & chills.
   b- Somnolescence, confusion & seizures.
   c- Alopecia.
   d- Anorexia, weight loss & Fatigue.
   e- Bone marrow inhibition → Granulocytopenia & thrombocytopenia.

Classification of Antimicrobials

* *According to Mechanism of Action:*

1- Inhibition of Cell Wall Synthesis:

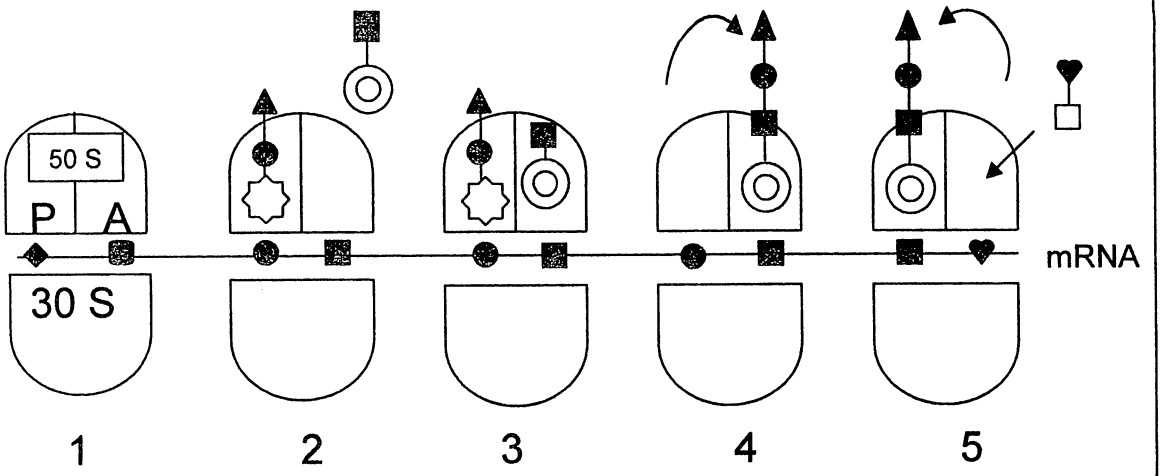
1- Cycloserine, Vancomycin & Bacitracin → ↓ Synthesis of peptidoglycan units → ↓ Inhibit early steps in cell wall synthesis.
2- β-Lactam Antibiotics (Penicillins & Cephalosporins)→ ↓ Transpeptidase enzyme → ↓ Cross-linking of peptidoglycan units → ↓ Late steps in cell wall synthesis.

2- Cytoplasmic Membrane:

1- Polymixins → Attach to phospholipids. It is a Cationic detergent.
2- Polyene antibiotics (Nystatin & Amphotericin) → Attach to ergosterols of fungal cell membrane → ↑ Permeability = Detergent-Like effect.
3- Azoles (Miconazole) → They combine with fatty acids of fungal *cell membrane* → ↓ Synthesis of ergosterols.

3- Protein Synthesis:

1- **Tetracyclines** bind to 30 S ribosomal subunit → Compete with tRNA for A site on mRNA-Ribosomal complex.
2- **Aminoglycosides** (Streptomycin) bind to 30 S ribosomal subunit → Abnormal codone / anticodone recognition → Misreading of mRNA.
3- **Chloramphenicol** binds to 50 S ribosomal subunit → ↓ Transpeptidation.
4- **Macrolids** (Erythromycin), Clindamycin, Fusidic acid & Spectinomycin bind to 50 S ribosomal subunit → ↓ Translocation.



1- Ribosomal subunits.
2- Arrival of Amino-acyl tRNA
3- Codone / Anticodone recognition → Reading of mRNA.
4- Transamination → Release of Old tRNA.
5- Translocation from A to P site → Free A site ready for new tRNA.
6- Shift of mRNA.

4- Nucleic Acid Synthesis:

1- **Folate Antagonists**:
   a- Sulfonamides: Compete with PABA. ↓ Dihydro-Pteroate Synthetase → ↓ Synthesis of folic acid.
   b- Trimethoprim: ↓ DHFA Reductase → ↓ Synthesis of Folinic acid (THFA).
2- **↓ DNA Polymerase**: Actinomycin D (Anti-Cancer) & Acyclovir (Anti-Viral).
3- **↓ RNA Polymerase**: Rifampicin.
4- **↓ DNA Gyrase (Topoisomerase II)**: Quinolones & Fluoroquinolones.

* *According to Their Spectrum:*

1- ***Narrow*** spectrum → Penicillin G, Erythromycin & Aminoglycosides.
2- ***Broad*** spectrum → Ampicillin, Cephalosporins, Chloramphenicol & Tetracyclines.

* *According to Their Effect:*

1- Bacteri***cidal***: β-Lactam antibiotics, Aminoglycosides, Polymixins & Quinolones.
2- Bacterio***static***: Tetracyclines, Chloramphenicol & Erythromycin low concentration

Antimicrobial Combinations

* Advantages:

1- To treat *Emergency* treatment of serious infections before bacteriological diagnosis.
2- To treat *Mixed* infections.
3- To delay emergence of *resistant* strains on chronic treatment e.g. TB.
4- Enhancement of antimicrobial activity → *Synergism*:
   a- Blocking successive steps in metabolic sequences e.g. TMP + SMX.
   b- One drug inhibits enzymes that destroy the other:
      i- Penicillin + Penicillinase inhibitor.
      ii- Imipenem + Cilastatin.
   c- One drug promotes the entry of the other into the microbe e.g. Penicillin + Aminoglycosides.
5- *Broaden the spectrum* e.g. Penicillin + Aminoglycosides.
6- To decrease *Adverse Effects* e.g. Triple sulfa.

* Disadvantages:

1- *Antagonism*: Usually bacteriostatic # bactericidal.
   e.g. Chloramphenicol + Aminoglycosides & Sulfa + Penicillin.
2- Increased adverse effects. Cephalosporin + Aminoglycosides → ↑ Ototoxicity.
3- Increased cost.
4- Interference with proper diagnosis.

* Outcome → Usually:

1- Static + Static → Addition.
2- Cidal + Cidal → Synergism.
3- Static + Cidal → Antagonism.

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Important Adverse Effects of Anti-Microbials

1- Penicillins → Allergy → Anaphylactic shock.
2- Cephalosporins → Nephrotoxicity.
3- Vancomycin → Red-man syndrome.
4- Aminoglycosides → Ototoxic, Nephrotoxic & N-M block.
5- Chloramphenicol → Bone marrow depression & Gray baby syndrome.
6- Tetracyclines → Teeth & bone abnormalities & Fanconi's syndrome.
7- Sulfa → Crystaluria.
8- TMP → Megaloplastic anemia.
9- Quinolones → Arthropathy.
10- Rifampicin → Orange discoloration or urine, tears, saliva, sweat & sputum.

Resistance To Anti-Microbial Drugs

* Types of Resistance:

A) Non-Genetic:

1- Metabolically inactive & non-multiplying organisms. } e.g. T.B.
2- Intra-cellular organisms. }
3- Absence of target site of the Anti-Microbial → Mycoplasma → No peptidoglycan cell wall → Resistant to β-Lactam antibiotics.

B) Genetic:

1- Chromosomal: Spontaneous mutation.

2- R-Plasmid = Extra-Chromosomal DNA:

Plasmids pass from one bacteria to another by:
a- *Transduction* along bacterial virus or Bacteriophage.
b- *Transformation* by cell lysis → Release of plasmids.
c- *Conjugation* by physical contact between bacteria.
d- *Translocation (Transposition)* → Exchange of R-genes between one plasmid and another or chromosome within the bacterium.

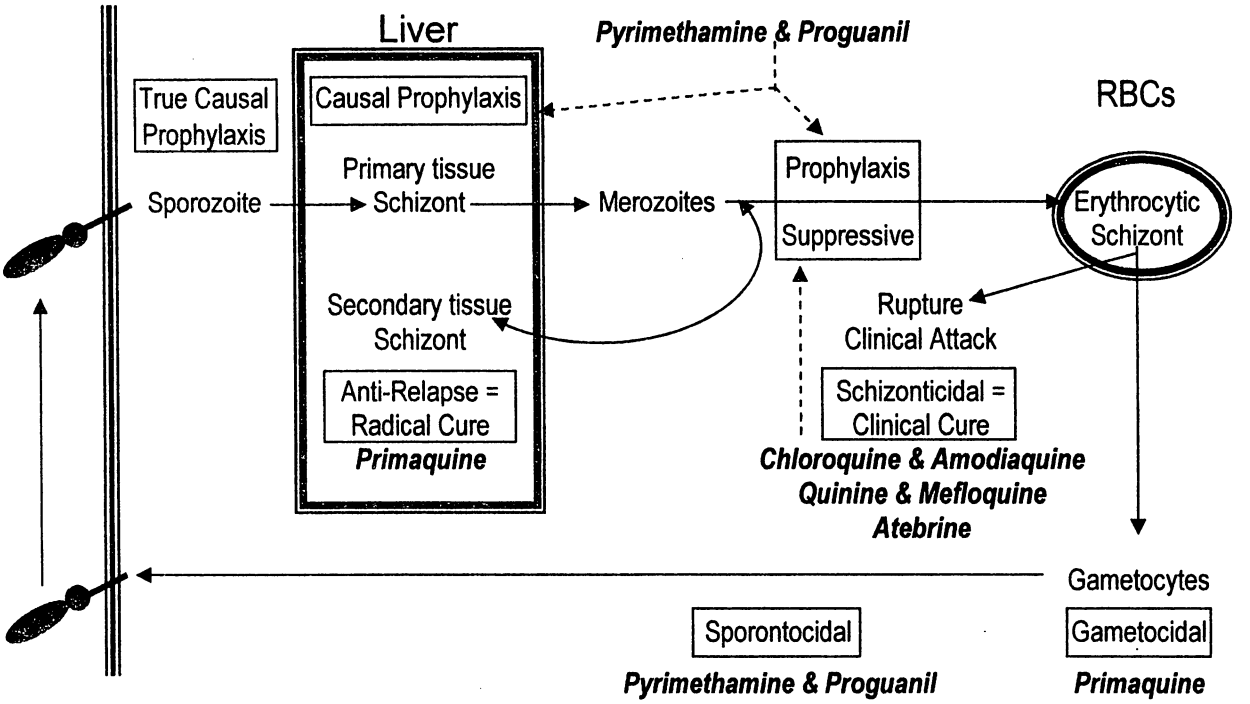
* Biochemical Mechanisms of Resistance:

1- Formation of *metabolizing enzymes* e.g. β-Lactamase.
2- ↓ *Uptake* of Anti-Microbial by bacteria.
3- Alteration or Deletion of *Target sites* e.g. Ribosomal subunits.
4- Change in sensitivity of *Target enzyme* e.g. Di-Hydro-Ptroate-Synthetase → ↓ Sensitivity to Sulfa *But Not* to PABA.
5- Development of Altered *Metabolic pathway* → Bacteria acquire Folic acid directly.

* Cross Resistance:

Resistance to one Anti-Microbial extends to another either with similar:
1- *Chemical nucleus* especially when resistance is due to metabolizing enzymes.
2- *Mechanism* of Action especially if resistance is due to alteration in Target site.

Chemotherapy of Malaria



NB) Plasmodium falciparum → No Secondary tissue schizont → No need for Primaquine.

* Anti-Malarial Drugs:

1- 4-Aminoquinolines: Chloroquine & Amodiaquine
2- 8-Aminoquinolines: Primaquine
3- Biguanides: Proguanil & Chlorproguanil.
4- Pyrimethamine. 5- Quinine & Mefloquine. 6- Atebrin (Quinqcrine).

*Choice Of Treatment:

A) Suppressive (Prophylaxis in Endemic Area):

Start one week before going to endemic area & continue for 4-10 weeks after returning back.

1- Pyrimethamine (First Choice): 25 mg Once / week orally.
2- Chloroquine: 500 mg Once / week orally.
3- Amodiaquine: 400 mg Once / week orally.
4- Proguanil: 100 mg / day orally.
5- Quinine: 300 – 600 mg / day orally.

B) Acute Attacks (Clinical cure = Blood Schizonticidal):

1- *Chloroquine phosphate Orally* (First Choice):
First day (Start by 1 g then after 6 hours 1/2 g) then 1/2 g in second & third days.
2- Amodiaquine Orally: 600 mg in First day then 400 mg in second & third days.

C) Radical Cure (Anti-Relapse):

1- All *Except* P. falciparum: Primaquine phosphate 15 mg/day for 14 days orally.
2- In P. falciparum either Chloroquine, Pyrimethamine or Proguanil. *No* need for Primaquine.

D) Emergency Malaria: Chloroquine HCl I.M.

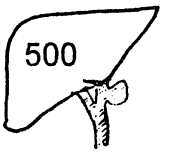
E) Chlroroquine-Resistant Plasmodium falciparum:

1- *Acute attacks* either:
a- Quinine 650 mg po tds X 7 days then Fansidar 3 tablets po once.
b- Quinine 650 mg po tds X 3 days then Tetracycline 250 mg qid po X 10 days.
c- Mefloquine 1 – 1.5 g po once.
2- *Prophylaxis*: Fansidar (Pyrimethamine 25 mg + Sulfadoxine 500 mg) Orally / week
OR Maloprim (Pyrimethamine 12.5 mg + Dapson 100 mg) Orally / week.

I- 4-Aminoquinolines:

1- Chloroquine Phosphate *(Resochin, Dagrinol, Cidoquin)*
2- Amodiaquine Hydrochloride *(Camoquin)*

*Pharmacokinetics:



1- Well absorbed orally.
2- Distributed All-over the body. Concentrated in liver 500 times > plasma.
3- Excreted in urine. Acidification of urine → ↑ Its excretion.

*Pharmacological Actions = Therapeutic Uses:

1- *Anti-Malarial*:
   a- Mechanism of Action → ↓ Enzymatic synthesis of D.N.A. & R.N.A.
   b- Erythrocytic (Blood) Schizonticidal:
      - Clinical cure → Followed by relapse *Except* in P. falciparum.
        Drug of Choice: In first day (1 g then after 6 hours 1/2 g) then 1/2 in days 2 & 3.
      - Radical cure in P. falciparum.
   c- Suppressive (Prophylaxis) → Suppresses merozoites before infecting RBCs.
      500 mg once / week Orally.

2- *Anti-Amebic ONLY* in Hepatic Amebiasis (250 mg X 3 X 3 weeks).

3- *Anti-Giardiasis*.

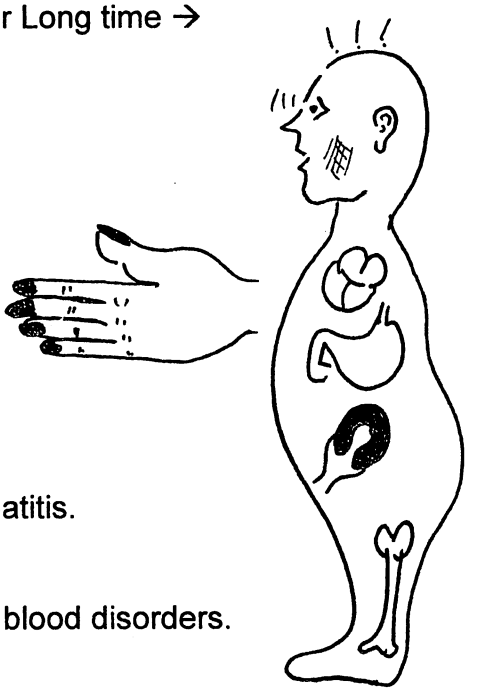
4- *Anti-Inflammatory* → Useful in Rheumatoid arthritis & lupus erythematosis.

5- Mild *Direct Myocardial Depressant* = Quinidine-like effect.

*Adverse Effects:

A) When used as Anti-Malarial → Small dose for short time → Almost NO adverse effects.

B) When used an Anti-Inflammatory → Large dose for Long time →



1- C.N.S. & Psychological disturbances.
2- Visual disturbances.
3- Ototoxicity.
4- Dermatitis → Desquamation, bleaching of hair, alopecia & thinning of nails.
5- Allergic manifestations.
6- Cardiotoxicity.
7- G.I.T. upsets.
8- Teratogenicity.
9- Bone marrow inhibition.

*Contra-indications:

1- With phenylbutazone or Gold therapy → Severe dermatitis.
2- Intermittent porphyria.
3- Pregnancy.
4- History of C.N.S., Skin (psoriasis), cardiac, hepatic or blood disorders.

II- Primaquine:

1- 8-Aminoquinoline.

2- Well absorbed orally → Liver → Active metabolite.

3- *Primary Tissue Schizonticidal*: *BUT* too toxic to be used in Chemo-prophylaxis.

4- *Secondary Tissue Schizonticidal* = *Radical cure* = *Anti-relapse*
In ALL forms *Except* P. falciparum. 15 mg / day for 14 days.

5- *Gametocidal*.

6- *Adverse Effects*:
a- Met-Hb & Hemolysis in patients with Glucose-6-Phosphate Dehydrogenase deficiency.

Primaquine → Met-Hemoglobin —(*Met-Hb Reductase + N.A.D.P.H.*)→ *Hemoglobin*

N.A.D.P. —(*Glucose-6-Phosphate Dehydrogenase*)→ *N.A.D.P.H.*

b- Small dose → Leukocytosis, while large dose → Leukopenia.
c- G.I.T. disturbances.
d- Atebrine & Proguanil → ↑ Primaquine toxicity → Toxic synergism.

III- Dihydro-Folate Reductase Inhibitors:

1- Biguanides: Proguanil & Chlorproguanil *(Chloroguanide)*.
2- Pyrimethamine *(Daraprim)*.

P.A.B.A. —(*D.H.P.S.*; *# Sulfa*)→ Folic Acid —(*Dihydrofolate Reductase*; *# TMP, Proguanil & Pyrimethamine*)→ Folinic acid.

* *Pharmacological Actions = Therapeutic Uses*:

1- Well absorbed orally → Active Metabolites → ↓ Dihydrofolate reductase →
↓ Conversion of Folic to Folinic acid.
2- Potentiated by sulfonamides:
a- Fansidar = Pyrimethamine + Sulfadoxine.
b- Co-Trimoxazole = Trimethoprim + Sulfamethoxazole.
3- Primary tissue schizonticidal + Suppressive → Chemo-prophylaxis of Malaria.
Pyrimethamine is the *Drug of Choice*: 25 mg once / week orally.
4- Sporotocidal → ↓ Fertility of Gametocides → ↓ Sexual cycle in Mosquito.
5- Erythrocytic schizonticidal *BUT* weaker & slower than Chloroquine.

*Adverse Effects:

1- Megaloplastic anemia → Treatment by Folinic acid.
2- Proguanil → ↑ Toxicity of Promaquine → Toxic synergism.
3- Resistance & Cross-resistance between them-selves & sulfa.

IV- Quinine:

Cinchona bark alkaloid. The L-isomer of Quinidine.

*Pharmacokinetics:

1- Well absorbed orally → Distributed All-over the body → Metabolized in liver.
2- Excreted in urine. Acidification of urine → ↑ Its excretion.

*Pharmacological Actions:

A) Anti-Malarial:

1- Suppressive → Inhibits Merozoites before infecting R.B.Cs.
2- Erythrocytic Schizonticidal: Protoplasmic poison → ↓ O_2 & CHO metabolism.

B) Other Actions:

1- Anti-pyretic analgesic.
2- Local irritant then local anesthetic.
3- Stomachic.
4- Direct myocardial depressant.
5- Oxytocic.
6- Curare like.

* Therapeutic Uses:

1- Suppressive, clinical cure & radical cure of Chloroquine-resistant P. falciparum.
2- I.V. in Cerebral malaria.
3- Anti-pyretic analgesic.
4- Sclerosing agent in Varicose veins.
5- Stomachic.
6- Myotonia congenita & nocturnal leg cramps.

* Adverse Effects:

1- Cinchonism (Similar to Salicylism) → Blurring of vision, tinnitus, C.N.S. & G.I.T. disturbances → Reversible on stopping Quinine.
2- Idiosyncrasy → Hemolysis → Black water fever.
3- Hypersensitivity.
4- Abortion.

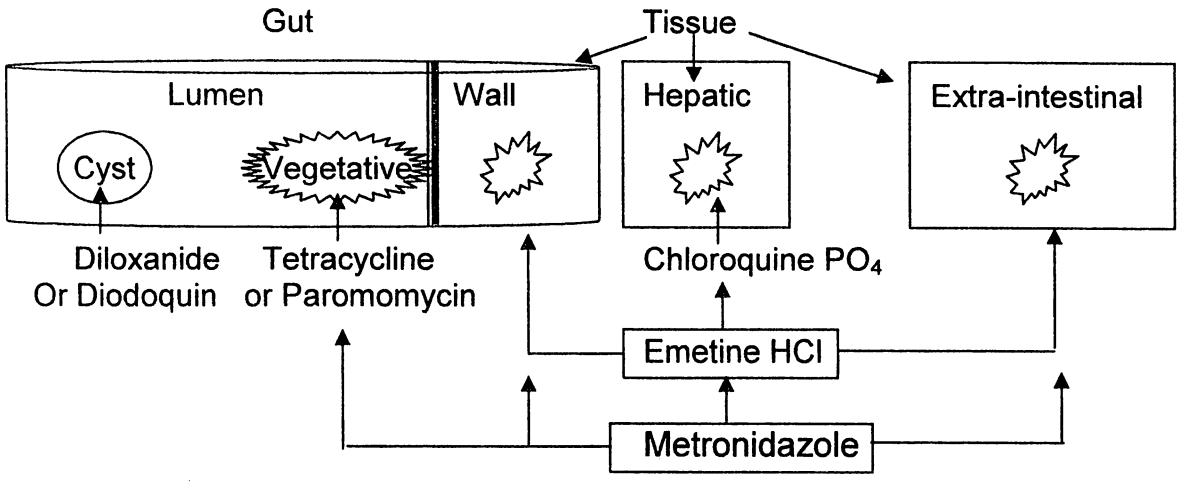
V- Mefloquine:

1- Related to Quinine.
2- Potent Erythrocytic schizonticidal.
3- Used ONLY in Chloroquine-Resistant P. falciparum. Either alone or with Fansidar.

VI- Atebrine (Quinacrine):

1- Anti-Malarial effect similar Quinine.
2- Anti-Giardiasis.
3- Anti-Tenia solium *(Pork tape worm).*
4- Causes yellow discoloration of skin.
5- ↑ Toxicity of Primaquine → Toxic synergism.

Chemotherapy of Amebiasis



Anti-Amebic Drugs

A) Luminal Amebicides (Bowel Lumen):

1- Diloxanide furoate *(Furamide)*:

a- Direct Amebicide.
b- Used in Asymptomatic cyst carrier (Cyst passer).
c- May cause flatulence.

2- Halogenated 8-Hydroxyquinolines;

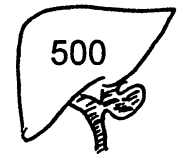
a- Di-iodo-hydroxy-quin (Diodoquin, Iodoquinol).
b- Iodo-chloro-hydroxy-quin (Vioform, Clioquinol).

3- Antibiotic Amebicides:

a- Paromomycin *(Humatin) po* → Aminoglycoside → Direct Amebicidal.
b- Tetracycline po → ↓ Flora → Starvation of ameba → Indirect Amebicide.

B) Tissue Abebicides:

1- Emetine HCl & Dehydroemetine: Gut wall, hepatic & extra-intestinal.
2- Chloroquine PO_4: Hepatic amebiasis *ONLY*.



C) Mixed Amebicides (Luminal + Tissue):

1- Metronidazole *(Flagyl)* } - *Gut Lumen + Wall*
2- Tinidazole *(Fasigyn)* } - *Hepatic + Extra-intestinal*

*Choice of Treatment:

A) Asymptomatic Cyst Carrier:

1-Diloxanide: 500 mg X 3 time X 10 days Orally
2-Diodoquine: 650 mg X 3 time X 21 days Orally, may be repeated

B) Mild Amoebic Colitis:

1-Metronidazole 750 mg X 3 times X 7-10 days Orally **+ *Diloxanide or Diodoquine.***
(Children: 35-50 mg/kg/day in divided 3 doses X 10 days)
2-Tetracycline 250-500 mg / 6 hours X 10 days **+ *Diloxanide or Diodoquine***

C) Severe Amoebic Dysentry:

Correct Dehydration & electrolyte disturbances ± Antimotility drugs
1-Metronidazole (I.V. then Oral) **+ *Diolxanide or Diodoquine***
2-Emetine HCl deep S.C. or I.M. 60 mg / day
then Tetracyclines po **+ *Diloxanide or Diodoquine***

D) Amoebic Hepatitis:

1-Metronidazole (I.V. or Oral) + Chloroquine 250 mg X 3 times X 21 days
+ *Diloxanide or Diodoquine*
2-Emetine HCl then Tetracycline + Chloroquine **+ *Diloxanide or Diodoquine***

I- Halogenated 8-Hydroxyquinolines:

*Preparations:

1- Iodo-chloro-hydroxyquin (Vioform , Clioquinol):

a- Partially absorbed orally:
- Attacks ameba from luman & blood stream → More effective than Diodoquin.
- More toxic than Diodoqin.

b- Dose: 0.75 – 1 g / day for 10 days po.

2- Di-iodo-hydroxy-quin (Diodoquin, Iodoquinol):

a- Not absorbed orall:
- Attacks ameba from lumen only → Less effective than Vioform.
- Less toxic than Vioform.

b- Dose: 1.5 – 2 g / day for 21 days po.

*Therapeutic Uses:

1- Intestinal amebiasis *oNLY*. Effective against *BOTH* cyst & motile forms.
2- Vioform → Trichomonas vaginalis.
3- Diodoquin → Giardia lamblia.

*Adverse Effects:

1- Vioform → Subacute Myelo-Optic Neuropathy (SMON syndrome).
2- Allergy. 3- Agranulocytosis.
4- G.I.T. upsets. 5- Liver damage.
6- Thyroid dysfunction.

*Contraindications:

1- Allergy to iodine. 2- Liver disease. 3- Thyroid diseases.

III- Nitrothiazoles:

A) Metronidazole *(Flagyl, Flazol, Amrizol, Flagicure, Metrozole, Elyzole)*

* Actions & Uses:

1- Reduced by anaerobic bacteria and protozoa → Active metabolite → Binds to DNA → ↓ Nucleic acid formation.

2- **Anti-Amebic** → Direct Amebicidal:
   a- *Tissue Amebicidal* (Gut wall, Hepatic & Extra-intestinal) :
      - Drug of CHOICE in Amebiasis (Intestinal, Extraintestinal & Hepatic).
      - Dose Adults : 750 mg tds Orally for 5-10 days.
        Children : 35-50 mg/kg/day for 7 days.
   b- *Less effective* as Luminal Amebicide. It is rapidly absorbed → Low Intra-Intestinal luminal concentrations.

3- **Anti-Trichomoniasis**: Drug of CHOICE.
   Adult Dose : 2 g Single Oral dose or 250 mg tds Orally for 7 days + Topical gel (0.75%) or vaginal suppository (500-1000 mg)

4- **Anti-Giardiasis**: Drug of CHOICE. 2 g daily for 3 days or 250 mg tds Orally for 7 days.

5- Powerful **Bactericidal** against:
   a- Peptic ulcer associated with H. pylori (250 mg tds orally for 14 days).
   b- Pseumomembraneous colitis (Clostridium difficile).
   c- Sepsis caused by Anaerobic Bacteroids :
      - Postsurgical. - Septicemia. - Osteomyelitis.
      - Abscess of brain and lung. - Intra-abdominal & pelvic infections.
   d- Acute ulcerative gingivitis & dental infections (Fusobacterium).
   e- Anaerobic vaginitis (Gardnerrella vaginalis).

6- **Disulfiram-like** action.

7- **Sensitize** hypoxic tumor cells to ionizing radiation.

* Adverse Effects;

1- Allergy.
2- CNS : Headache, Dizziness & Vertigo.
3- GIT : Nausea, vomiting, diarrhea, furry tongue & Metallic taste in mouth.
4- Intensification of Moniliasis.
5- leukopenia.
6- Suppression of cellular immunity.
7- Mutagenic → Carcinogenic and/or Teratogenic.

B) Tinidazole *(Fasigen):*

Similar to Metronidazole BUT effective in Shorter courses.

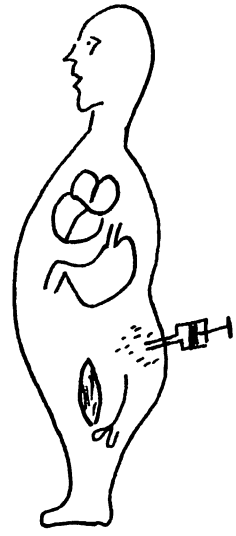
III- Emetine Hydrochloride:

1- Epicacuanha alkaloid.
2- Direct tissue amebicide → Gut wall, hepatic & extra-intestinal.
   It causes degenerative effects on cytoplasm & nucleus.
3- Effective against motile vegetative trophozoites rather than cysts.
4- Concentrated in liver.

* Therapeutic Uses:

1- Amebic dysentery.
2- Hepatic amebiasis & amebic abcess.
3- Ameboma & extra-intestinal amebiasis.

* Dosage:



1- Deep S.C. or I.M. 65 mg / day for 5 – 10 days.
2- Very irritant → Not given orally.
3- Cardiotoxic → Not injected I.V. & NOT repeated before 30 days.

* Adverse Effects:

1- C.V.S.: Toxic myocarditis & Hypotension.
   Bed rest during Emetine therapy with frequent E.C.G. tracings.
2- G.I.T.: Nausea, vomiting & diarrhea.
3- Local pain & tenderness at site of injection.
4- Skeletal muscle stiffness & tenderness.
5- Peripheral neuritis.

NB) Dehydroemetine: Similar to Emetine HCl *BUT* less toxic.

NB) Emetine Bismuth Iodide: *Was* used orally against cyst forms.

NB)

A-**Trichomoniasis**:

*1- **Metronidazole**:*
   a-Both partners: 2 g single oral dose or 250 mg X 3 X 7
   b-Topical gel (0.75%) or vaginal suppository
*2- **Tinidazole**: 2 g single oral dose*
*3- **Vioform**.*

B- **Giardiasis**:

*1-**Metronidazole**:*
   a-Adult dose: 2 g orally X 3 days or 25o mg X 3 X 7
   b-Cildren: 5 mg/kg X 3 X 7
*2-**Tinidazole**: 2 g single Oral dose*
*3- **Diodoquine**.*
*4- **Chloroquine PO_4**.*
*5- **Atebrine***

Chemotherapy of Schisosomiasis (Bilharziasis)

1- Praziquantel (Biltricide, Distocide & Cystocide)

* Anti-Helmintic Effects:

1- **Schitosomicidal**.
2- Effective against other *Trematodes* e.g. Heterophyes.
3- Effective against Cystodes e.g. Taenia solium & saginata, Hymenolepis nana & Diphyllobothrium latum.
4- ***NOT*** effective against Nematodes e.g. Ascaris & Ankylostoma.

* Schistosomicidal Effects:

1- **Mechanism of Action** → ↑ Ca^{2+} Influx → Severe contraction of worms →
   a- Spastic paralysis → Dislocation & Shift e.g. S. mansoni → Hepatic shift → Death & phagocytosis.
   b- Tear of tegument → Exposure of antigenic sub-tegumental structure → Immune response by the host.

2- Effective against **ALL** species of Schistosoma pathogenic to man.

3- Effective against **ALL** stages (Adult, immature e.g. cercaria & even the eggs).

4- Drug of **CHOICE** in S. mansoni, hematobium & mixed infections.

5- **Dose**: 40 mg/kg Once po or 20 mg/kg 3 doses in one day po.

6- **Advantages**:
   a- Drug of CHOICE in ALL species.
   b- High cure rate → 80 – 95 %.
   c- One day treatment.
   d- Tolerated & safe even in patients with advanced portal fibrosis.

7- **Disadvantages**:
   a- Shortly after administration → Headache, dizziness, abdominal pain & discomfort.
   b- After few days:
      - Drowsiness & low grade fever
      - Anorexia, nausea, vomiting & loose stool.
      - Arthralgia & myalgia.
   c- After several days → Release of proteins from dead worms → Host reaction → Rash & pruritus.

8- **Contraindications**:
   a- Pregnancy & lactation
   b- Children below 4 years.

2- Mirazid

1- Natural of plant origin → Pure *Commiphora* extract.
2- Anti-Schistosomal effect. Dose: 10 mg/kg Orally X 3-6 days → 92-98% cure rate.
   It induces muscle contraction with affection of tegument & tubercles.
3- Also effective in Fascioliasis. Dose 10 mg/kg Orally X 6 days → 100% cure rate.

3- *Oxamniquine* (Vansil)

1- Effective *ONLY* against Schistosoma **mansoni**.

2- **Mechanism of Action**:
   a- Selective uptake by *Male* worms → Activated inside the parasite → Alkylate D.N.A.
   b- Death on *Male* worms → Hepatic shift → Phagocytosis.
   c- Surviving unpaired *Female* return to mesenteric vessels *BUT Do NOT* lay eggs.

3- **Advantages**:
   a- Second drug of choice in S. mansoni:
      - Dose 20 mg / kg / day X 3 days po.
      - Cure rate → 70 -95 %.
   b- Easy oral administration.
   c- Safe & allowed in severe hepato-splenic diseases.

4- **Disadvantages**:
   a- C.N.S. → Dizziness, drowsiness, psychosis & seizures.
   b- G.I.T. → Nausea & diarrhea.
   c- Transient elevation of hepatic transaminase enzymes.
   d- Orange discoloration of urine.
   e- Eosinophilia & low grade fever due to Host reaction to dead worms.

5- **Contraindications**: Epilepsy & Pregnancy.

3- *Metrifonate* (Bilarcil)

1- Effective ONLY against Schistosoma ***hematobium***.
2- **Mechanism of Action**:
   a- Organophosphorus compound → Irreversible Anti-Ch.E. → Paralysis of worms
      →Shift to systemic circulation → Lung → Encased.
   b- Living eggs are found in urine for several months.
3- **Advantages**:
   a- **Second** drug of choice in treatment of S. hematobium.
      Dose: 7.5 mg / kg Orally X 3 dose / 2 weeks interval → Cure rate 50-90%.
   b- Easy oral administration.
4- **Disadvantages**:
   a- C.N.S.: Lassitude & vertigo.
   b- G.I.T.: Nasea & colic.
5- **Contraindications**:
   a- **NO** recent, within 48 hours, exposure to organophosphorus insecticides.
   b- **NO** use of succinylcholine for at least 48 hours.
   c- Pregnancy.

NB) Trivalent Antimonial Drugs e.g. **Tartar emetic I.V.** were used in treatment of Bilharziasis. They are *obsolete* nowadays because of their high toxicity that was treated by Dimercaprol (B.A.L.)

Treatment of Trematodes & Cystodes

Worm	Drug of Choice	Alternative
1-Bilharziasis	Praziquantel 40 mg/kg single oral dose or 20 mg / kg 3 doses in one day	Mirazid (Commiphora) 10 mg / kg X 3 – 6 days
2-Taenia solium	Praziquantel 10 mg / kg single oral dose	
3-Taenia saginata	Praziquantel 10 mg / kg single oral dose	Niclosamide 2 g on empty stomach then saline purge
4-Hymenolepis nana	Praziquantel 25 mg / kg single oral dose	Niclosamide 2 g after breakfast X 7 days

1-**Praziquantel** *(Biltricide, Bilharzid, Distocide, Belicide, Epiquantel & Praziquantel)*
2-**Niclosamide** *(Yomesan & Niclosan)*

Treatment of Nematods

Worm	Mebendazole	Flubendazole	Albendazole	Pyrantel pamoate	Levamisole	Piperazine
1-Ascaris "Round worm"	100 mg X 2 X 3	100 mg X 2 X 3	400 mg single dose	11 mg/kg max 1 g repeat after 2 weeks	150 mg od 3 mg/kg	3.5 g X 2 75 mg/kg X 2
2-Ankylostoma "Hook worm"	100 mg X 2 X 3	100 mg X 2 X 3	400 mg single dose	11 mg/kg max 1 g repeat after 2 weeks	150 mg od 3 mg/kg	
3-Oxyuris "Entrobius,Pin worm"	100 mg od repeat after 2 & 4 weeks	100 mg od repeat after 2 & 4 weeks	400 mg od repeat after 2 w	11 mg/kg max 1 g repeat after 2 & 4 weeks		2 g X 7 65 mg/kg X 7
4-Strongyloids "Thread worm	100 mg X 2 X 3	100 mg X 2 X 3	400 mg X 2 X 7 repeat after 2 weeks			
5-Trichuris "Whipworm"	100 mg X 2 X 3	100 mg X 2 X 3	400 mg single dose			

NB)

1- Anthelmintic drugs either kill the worm (**vermicide**) or expel the worm outside the intestine (**vermifuge**).

2-Ankylostoma: Treat iron deficiency anemia & improve general condition before anti-helmintics.

3-Oxyuris: Treat pruritus by ointment of white precipitate of mercury around anal and vulvar regions.

Chemotherapy of Helminthiasis

1- Ascaris Lumbricoides (Roundworm) :

1- Piperazine *(Antipar)* :

a- Dose : Single oral dose of 3.5 g for adults (75 mg/kg for children) on two successive days. 90% cure.
b- Mechanism : Curare-like → Paralysis of ascaris muscles → Expulsion → Vermifuge.
Active against : Ascaris & Oxyuris (Entrobius vermicularis).
c- Kinetics : Absorbed orally. Partially metabolized. Excreted in urine.
d- Contraindications : Epilepsy, liver and kidney diseases.

2- Pyrantel pamoate *(Combantrin)* : *Broad spectrum anthelmintic.*

a- Dose : Single oral dose of 11 mg/kg (maximum 1 g), may be repeated after 2 weeks.
b- Mechanism : Depolarizing N-M blocker & ↓ cholinesterase → Spastic paralysis of worm. Active against : Ascaris, Ankylostoma & Oxyuris but NOT Trichuris.
c- Kinetics : Poorly absorbed orally.
d- Toxicity : GIT upset & CNS → Headache and dizziness.

3- Mebendazole *(Vermox)* : *Broad spectrum anthelmintic.*

a- Dose : 100 mg orally morning and evening for 3 days.
b-Mechanism : Irreversible inhibition of glucose uptake by the parasite.
Active against : Ascaris, Ankylostoma, Oxyuris, Trichuris & Strongyloides → Useful in mixed infestations. Also against Hydatid disease, T. solium & T. saginata.
c- Toxicity : GIT upsets → Abdominal pain & diarrhea.
d- Contraindications : Pregnancy.

4- Flubendazole *(Fluvermal)* : *Broad spectrum anthelmintic* similar to Mebendazole.

5- Albendazole *(Zental)* : *Broad spectrum anthelmintic.*

a- Dose :
- Ascaris, Ankylostoma & Trichuris : 400 single oral dose with meal.
- Oxyuris : Repeat after 2 weeks.
- Strongyloides : 400 mg orally twice daily for 3-7 days, may be repeated after 2 weeks.

b- Mechanism : Similar to Mebendazole.
Active against : Ascaris, Ankylostoma, Oxyuris, Trichuris & Strongyloides. Also against Hydatid disease.
c- Kinetics : Absorbed orally, metabolized & excreted in urine.
d- Toxicity : GIT upsets & CNS → headache, dizziness, lassitude & insomnia.
e- Contraindications : Pregnancy & liver cirrhosis.

6- Levamisole *(Ketrax)* :

a- Dose : Single oral dose of 150 mg for adults & 3 mg/kg for children.
b- Mechanism : Anticholinesterase → Depolarizing N-M blocker & ↓ succinate dehydrogenase → Paralysis of worm.
Active against : Ascaris and Ankylostoma.
c- Immunostimulant : Useful in chronic and recurrent infections & rheumatoid arthritis.

2- Ankylostoma duodenale (Hookworm) :

1- Treatment of anemia by using iron preparations & improve general condition.
2- Anthelmintics :
   a- Pyrantel pamoate. b- Mebendazole. c- Flubendazole.
   d- Albendazole. e- Levamisole.

3- Oxyuris (Entrobius vermicularis , Pinworm) :

1- Treat pruritus ani by using ointment of white precipitate of mercury around anal and vulvar regions.
2- Anthelmintics :
   a- Pyrantel pamoate : 11 mg/kg (maximum 1 g) single oral dose repeated after 2 & 4 weeks.
   b- Mebendazole : 100 mg single oral dose, repeated after 2 & 4 weeks.
   c- Flubendazole. d- Albendazole.
   e- Piperazine : 2 g for adults (65 mg/kg for children < 30 kg) single oral dose for 7 days.

4- Trichuris trichiura (Whipworm) :

1- Mebendazole. b- Albendazole. c- Thiabendazole.

5- Strongyloides stercoralis (Threadworm) :

1- Thiabendazole *(Mintezol)* : *Broad spectrum anthelmintic.*
a- Dose : 50-60 mg/kg single oral dose or divided on 2 doses for 2 successive days.
b- Active against : Ascaris, Ankylostoma, Oxyuris, Trichuris & Strongyloides (drug of CHOICE).
c- Toxicity : GIT & CNS.

2- Mebendazole. 3- Albendazole.

6- Tapeworms (T. solium, T. saginata & Hymenolepis nana) :

1- Niclosamide *(Yomesan)* :
a- Dose :
   - Taenia saginata : 2 g (4 tablets X ½ g) chewed on an empty stomach.
     + Night before drug → No solid food + Saline purgative ($MgSO_4$).
     + 2 hours after drug → Saline purgative.
   - Hymenolepis nana : 2 g once daily after breakfast for 7 days.
b- Vermicidal against T. solium, T. saginata & H. nana. In case of T. solium → Cysticercosis.

2- Praziquantel :
1- T. solium & T. saginata : 10 mg/kg single oral dose.
2- H. nana : 25 mg/kg single oral dose.

7- Filariasis (Wucheraria bancrofti) :

1- Diethylcarbamazine *(Hetrazan)* :

a- Dose : 2 mg/kg tds after meals for 3 weeks.

b- Mechanism : Sensitizes microfilariae to phagocytosis by RES cells. Also it may kill adult worms.

c- Kinetics : Absorbed orally, metabolized & excreted in urine.

d- Side effects :

- Allergic manifestations due to killing large number of microfilariae. Antihistaminics or corticosteroids are used routinely in the first 4-5 days of treatment.
- Anorexia, nausea, vomiting & headache.

2- Ivermectin :

a- Potent antifilarial. It potentiates GABA → N-M block → Paralysis of worm.

b- Side effects : Headache, fever, skin rash, muscle & joint pains.

Adverse Reactions To Anti-Microbials

A) Resistance.

B) Superinfection:

1- Pseudo-membranous (Antibiotic-associated) colitis induced by enterotoxins of Clotridium dificil & Staph. Treatment by *Oral* Metronidazole or Vancomycin.

2- Moniliasis (Candidiasis) treated by Nystatin.

C) Hypersensitivity (Allergic) Reaction:

1- Manifestations → Ranges from mild Skin rash & Urticaria up to Angio-edema & Anaphylactic shock.

2- Cross Allergy between related drugs e.g. Penicillins & Cephalosporis.

D) Idiosyncrasy:

1- Hemolytic anemia in patients with Glucose-6-Phosphate-Dehydrogenase Enzyme Deficiency induced by Primaquine & Sulfonamides.

2- Slow and Rapid acetylators of Isoniazid.

E) Direct Toxicity:

1- Nervous system:
   a- C.N.S. excitation and seizures → Penicillins & Quinolones.
   b- Pseudo-tumor cerebri → Minocycline.
   c- Peripheral neuritis → Isoniazid & Nitrofurantoin.

2- Opto-toxicity → Chloramphenicol, Ethambutol & Chloroquine.

3- Oto-toxicity → Aminoglycosides & Chloroquine.

4- Skin affection → Sulfones & Chloroquine .

5- Cardio-toxicity → Tartar emetic & Emetine HCl.

6- G.I.T. disturbances:
   a- Irritation → Tetracyclines.
   b- Teeth affection → Enamel dysplasia → Tetracyclines.

7- Hepato-toxicity:
   a- Hepato-cellular damage → Sulfonamides & Tetracyclines.
   b- Cholestatic jaundice → Erythromycin *esteolate*.

8- Nephro-toxicity → Cephalosporins, Aminoglycosides, Tetracyclines (*Fanconi's syndrome*), Tetracyclines & Sulfonamides.

9- Teratogenicity → Tetracyclines.

10- Skeletal muscle → N-M block → Aminoglycosides.

11- Bone → Tetracyclines.

12- Cartilage → Fluoroquinolones.

13- Bone marrow & Blood:
   a- Bone marrow inhibition → Chloramphenicol & Sulfonamides.
   b- Hemolytic anemia → Sulfonamides & Primaquine.
   c- Megaloplastic anemia → Trimethoprim.
   d- Thrombophlebitis → Cephalosporins.

Cancer Chemotherapy

1- NO qualitative differences between cancer & normal cells.
2- There is quantitative differences. Malignant cells have :

a- Rapid and uncontrolled rates of MITOSIS.
b- Rapid turn over of NEUCLEOPROTEINS.
c- High Anabolic & Low Catabolic enzyme activity.
d- High DEPHOSPHORYLATING activity.

* Anti-Cancer Drugs :

1- Anti-Metabolites.
2- Alkylating Agents.
3- Hormones & Antagonists.
4- Radioactive Isotopes.
5- Natural Products :

a- ***Plant Alkaloids*** :
- Vinca Alkaloids : Vinblastin & Vincristine : IV in Hodgkin's disease
- Colchicine & Demecholcine : Also effective in Acute Gout.

b- ***Antibiotics*** : Actinomycin-D (Dactinomycin) : IV in Wilm's tumor of the kidney.
Other antibiotics : Mithramycin & Bleomycin.

c- ***Enzymes*** : L- Asparaginase enzyme.

d- ***Interferons*** : Alpha-2a & Alpha-2b : in Kaposi's sarcoma of AIDS.

6- Miscellaneous :

a- ***Cisplatin*** : Inorganic platinum complex.

b- ***Mitotane & Aminoglutethimide*** : In Adrenocortical carcinoma & Cushing.

1- Anti-Metabolites :

- Similar to Normal metabolites = **Analogues.**
- Compete with Normal metabolites = **Antagonists.**
- They inhibit the synthesis of **NUCLEIC ACID.**

A) *Folic Acid Antagonists (Analogues)* : **Methotrexate**.

1- Non-competitive Antagonist of Di-Hydro-Folate Reductase (DHFR) enzyme.
2- Produces Megaloplastic anemia, treated by FOLINIC acid ONLY.
3- Pharmacokinetics :
a- Absorbed orally. b- Concentrated in liver & kidney.
c- 50% Excreted unchanged in urine within 48 hr.
4- Therapeutic Uses :
a- Acute lymphocytic leukemia in children : 2.5-5 mg/day orally for 3 weeks or till manifestations of remission or toxicity appear.
b- Chorionic epithelioma. c- Severe psoriasis.
d- As an immunosuppressive e.g. in Rheumatoid disease.

B) *Pyrimidine Antagonists (Analogues)* : **5- Fluorouracil** IV.

C) Purine Antagonists (Analogues) : **6-Mercaptopurine**.

1-Allopurinol inhibits the metabolism of 6-Mercaptopurine → Toxicity.
2-Used ORALLY in :
a- Acute lymphocytic leukemia in children.
b- As an Immunosuppressive in tissue transplantation.

2- Alkylating Agents :

- Highly reactive, they react chemically with nucleoproteins.
- Similar effects to that of XC-ray.

1- Nitrogen Mustards :

a- **Mechlorethamine** *(Nitrogen Mustard, Mustin & Mustergen)* :
IV (Very irritant), Fresh solution (Unstable) in Hodgkin's disease.
b- **Cyclophosphamide** *(Endoxan)*: Prodrug, activated by dephosphorylation. PO & IV.
c- **Chlorambucil** *(Leukeran)* : Orally, drug of CHOICE in Chronic lymphatic leukemia.
d- **Melphalan** *(Alkeran)* : Orally in Multiple myeloma.

2- Alkyl Sulphonates :

- **Busulphan** *(Myleran)* : Selective on Bone Marrow. Orally in Chronic myeloid leukemia.
- NO effect on GIT or Lymphoid tissues.

3- Nitrosurea :

a- **Carmustin.**
b- **Lomustin.**
c- **Semustin.**

- Lipid soluble.
- Pass BBB.
- Useful in Meningeal leukemias & Brain tumors.

* Toxicity of Anti-Metabolites & Alkylating Agents :

Most of the toxic manifestations are MAINLY due to affection of the NORMAL RAPIDLY MULTIPLYING CELLS e.g. Skin, bone marrow, GIT mucosa & Gonads.

1- Skin & M.M. : Alopecia, dermatitis & Vesication.
2- C.N.S. : Convulsions & Coma.
3- Vomiting : Treated by Dexamethasone + Metoclopramide or Domperidone ± Ondansetron (5-HT_3 blocker) or Nabilone (Cannabinoid) or Lorazepam.
4- G.I.T. : Ulcerations.
5- Liver & Kidney Damage e.g. Urate nephropathy (prevented and treated by Allopurinol).
6- Hemorrhagic **Cystitis**.
7- Gonads : ↓ Oogenesis, ↓ Spermatogenesis & Mutations → Teratogenicity.
8- BONE MARROW APLASIA → MOST DANGEROUS :
a- If Mild → Reduce the dose of the Anti-Cancer drug.
b- If Severe : - Stop the Anti-Cancer drug.
- Fresh blood transfusion & Platelet transfusion.
- Bactericidal antibiotics.
c- Recombinant Erythrobiotin & Granulocyte-Myelocyte Colony Stimulating Factors (GM-CSF) may be used.

3- Hormones & Analogues :

1- **Cortisol** : Acute lymphocytic leukemia & Malignant lymphomas.

2- **Estrogens** Male cancer prostate & Female late post-menopausal (*Non-Estrogen Dependent*) cancer breast.

3- Anti-Estrogens e.g. ***Tamoxifen*** in pre-menopausal *(Estrogen-Dependent)* cancer breast

4- **Androgens** in Pre-menopausal cancer breast.

5- Anti-Androgens e.g. ***Flutemide*** in cancer prostate.

6- Gonadotrophin Releasing Hormone Analogue e.g. ***Leuprolide*** in cancer prostate.

7- ***Progestins*** in endometrial carcinomas.

4- Radio-Active Isotopes :

1- ^{131}I :	- $t_{1/2}$ = 8 days.	- Beta & Gamma rays.	- Cancer thyroid.
2- ^{198}Au :	- $t_{1/2}$ = 2.7 days.	- Beta & Gamma rays.	- Malignant effusions.
3- ^{32}p :	- $t_{1/2}$ = 14.3 days.	- Beta ray ONLY.	- Polycythemia.

Miscellaneous

Geriatric Pharmacology

* General considerations:

1- In **elderly** there is:
   a- ↓ **Lean** body mass
   b- ↓ Total and percentage of body **water**
   c- ↑ **Fat** as a percentage of body mass
   d- ↓ Serum albumin
   e- ↑ Serum α-acid glycoprotein.
2- **Metabolic** reactions carried out by mixed function oxidase system CYP-450 (phase 1 reactions) are affected to greater extent than phase II reactions (Conjugation).
3- **Renal** elimination is decreased with age.
4- There is high incidence of **adverse** effects in elderly due to polypharmacy, reduced drug elimination, multiple disease states and increased drug sensitivity.
5- **Other problems** in elderly are patient compliance, memory changes, hear loss and decreased vision.

* Pharmacokinetics in geriatrics:

1- **Absorption** can be affected due to:
   a- Delayed gastric *emptying*, elevated gastric *pH* and impaired intestinal *motility*.
   b- Decreased splanchnic *blood flow*.
   c- *Rate* of absorption is affected *BUT Extent* of absorption is rarely affected.
2- **Distribution** :
   a- Due to ↓ **body water** the Vd of water soluble drugs as paracetamol is decreased.
   b- Due to ↑ **Fat** as a % of body mass Vd of fat soluble drugs as diazepam is increased.
   c- Due to ↓ **Albumin** with age → ↑ Free fraction of some drugs as warfarin.
3- **Elimination** (metabolism and excretion) :
   a- **Metabolism** → **Reduced** hepatic *blood flow* and **decreased** activity of *microsomal* enzymes.
   b- **Renal** elimination is **decreased** → ↑ Plasma level of Digoxin, H_2 antagonists & Aminoglycosides.

   → - ↓ Elimination of Drugs →
   - ↑ Their plasma level →
   - Accumulation →
   - ↑Their adverse effects.

* Pharmacodynamics in geriatrics:

1- **Altered receptor sensitivity** e.g. there is diminished response to β-blockers.
2- **Exaggerated response** to certain drugs as Analgesics, Warfarin, Benzodiazepines.
3- **Decreased baro-receptor** sensitivity can increase the risk of postural hypotension.

** Very Important in Geriatrics:* (هام جدا)

1- Start treatment by a low dose,
2- Use minimal number of drugs
3- Always evaluate possible drug toxicity.

Vitamins

* *Classification* :

1- Fat Soluble : A , D , E & K.
2- Water Soluble : B complex & C.

NB) Vit K, B-12 & Folic acid (See Blood), Vit D (see Hormones)

Vit B_1 (Thiamine)

1- Coenzyme (Co-Carboxylase) → Important for CHO metabolism.
2- Deficiency → **Beri Beri** → Dry (Neuritis) or Wet (Heart Failure with edema).
3- *Uses* : Treatment & Prophylaxis of Beri Beri.

Vit B_2 (Riboflavin)

1- Flavoprotein → Hydrogen carrier.
2- Deficiency → Sore throat, angular stomatitis, dermatitis, anemia, neuropathy.
3- Uses : Treatment & Prevention of Multiple nutritional deficiency.

Vit B_6 (Pyridoxine)

1- Coenzyme in amino acid metabolism.
2- Deficiency :
   a- Nutritional deficiency.
   b- *Drug induced : Isoniazid, Hydralazine & Procainamide.*
   c- Manifestations : Dermatitis, *Peripheral Neuritis*, Convulsions & Anemia.
3- Uses :
   a- Combined treatment of any Vit B deficiency.
   b- Prophylactic with Isoniazid, Hydralazine & Procainamide.
   c- Treat Vomiting of Pregnancy.
   d- Treat Depression in Pregnancy & Oral contraceptives.

Vit B_7 (Niacin)
Nicotinic Acid & Nicotinamide

1- Nicotinamide is a constituent of coenzyme I (NAD) & coenzyme II (NADP) → H^+ carrier.
2- Deficiency → **Pellagra** = 3 Ds (Dermatitis, Diarrhea & Dementia)
3- Uses :
   a- Treatment & Prevention of Pellagra.
   b- Vasodilator.
   c- Hypocholesterolemic & Hypolipidemic.

Vit C (Ascorbic Acid)

* *Importance* :

1- Synthesis of collagen.
2- Integrity of intercellular matrix and Capillary wall.
3-In Adrenal gland :
   a- Cortex : Synthesis of corticosteroids.
   b- Medulla : Prevent oxidation of Adrenaline.
4- Important for metabolism of Folic acid, Tyrosine & CHO.
5 **Anti-Oxidant** :
   a- Eye → # Cataract.
   b- ↓ Risk of mortality of ischemic heart disease (IHD).
   c- ↓ Cancer specially Gastric.

* *Deficiency* → **Scurvy :**

1- Bleeding swollen gums with loose teeth.
2- Hemorrhages in the skin, muscle & bone.
3- Anemia.
4- Low resistance → Infections & ↓ wound healing.

* *Indications* :

1- Prevent & Treat scurvy (1 g/day).
2- Met-Hb.
3- ↑ Iron absorption.
4- Acidification of urine in
   a- Urinary Tract infection.
   b- Help excretion of weak basic drugs e.g. amphetamine & ephedrine.
5- Large doses may be useful for prevention of :
   a- Cataract. b- Common cold.
   c- Hypercholesterolemia. d- Some types of cancer.

* *Side Effects of Vit C* :

1- LD for Long time → Sleep disturbances, headache, GIT upsets & Oxalate stones.
2- I.V. → Hemolytic anemia in G6PD deficiency.

Vit A (Retinol)

* Nature : Unsaturated alcohol.

1- **Retinol** (Vit A-1) : Present in liver of sea-water fish.
2- **Dehydroretinol** (Vit A-2) : Present in liver of fresh-water fish. Weaker than Vit A-1.
3- **Carotenes** plant pigments (Provitamin A) → Intestinal mucosa + Vit B-12 → Vit A.

* *Importance* :

1- Retina : Component of rhodopsin which is important for dim light vision.
2- Growth & development of epithelium & bone.
3- Anti-oxidant : ↑ Immune system & ↓ Malignancy.

* *Deficiency of Vit A* :

1- Eye : Night blindness (***Nyctalopia***) & Xerophthalmia.
2- Skin : Hyperkeratosis.
3- ↑ Incidence of respiratory infections.
4- ↑ Incidence of squamous metaplasia.

* *Indications of Vit A* :

1- Treatment of Deficiency.
2- During pregnancy, lactation & infancy.
3- Low resistance.
4- Large dose in dyskeratotic skin disease e.g. Psoriasis & Acne
5- Prevention of some cancers.

* *Adverse Effects of Vit A* :

1- Skin lesion & Hair loss.
2- Anorexia & Hepato-splenomegaly.
3- Painful tender swelling of long bones.
4- Teratogenic.

* *Preparations* :

1- Retinol : Oral Capsules.
2- Tretinoin : Topically in Acne.
3- Isotretinoin ($t_{1/2}$ = 20 hr) : Orally in sever Acne.
Teratogenic. Use contraceptives for 4 WEEKS.
4- Etretinate ($t_{1/2}$ = 90 Days) : Orally in Psoriasis.
Teratogenic. Use contraceptives for 2 YEARS.

Vit E (Tocopherols)

Tocopherols (α,β & γ) are present in wheat germ oil, green vegetables, egg & meat.

* *Importance* & Indications :

1- Anti-Oxidant :
   a- Potent fat-soluble antioxidant specially against peroxidation of cellular & sub-cellular membranes and phospholipids.
   b- Concentrated at regions exposed to highest PO_2 e.g. RBCs & membranes of Respiratory tract.
2- Prevents oxidation of LDL → ↓ Atherosclerosis → ↓ Risk of mortality from IHD by 75%.
3- Treat & prevent Liver cirrhosis.
4- Treat & prevent Anemia. Supplement in pregnancy, lactation & old age.
5- Treat some muscle dystrophy diseases.
6- Anti-sterility factor *(In animals)*. Tried in habitual abortion & sterility.
7- Treatment of some cancers.

* *Deficiency* :

1- Peripheral neuritis & spino-cerebellar degeneration.
2- Hemolytic anemia in premature infants.

Oxidants & Anti-Oxidants

* Oxidants :

1- ***External Agents*** : Cigarette smoke, Air pollution, U.V. rays, Ozone, Irradiation, Sulfur oxide, Solvents, Asbestos & Pesticides.

2- ***Internal Metabolic (Free Radicals)*** : Compounds containing an unpaired electron & react very quickly with other compounds to steel their electrons → Create new free radicals.
   a- Common Examples : Hydroxyl, superoxide and lipid peroxide radicals.
   b- They have beneficial role in fighting off infection e.g. macrophages.
   c- Harmful Effects → Damage complex molecules :
      - Proteins → Cataract, aging of skin, and insult to liver & kidney.
      - Lipids → Damage of cell membrane → Atherosclerosis → IHD & Stroke.
      - DNA → Mutation & Cancer formation.

* Biological Antioxidants :

1- ***Enzymes*** : Superoxide dismutase, catalase & Glutathione peroxidase.

2- ***Vitamins*** : C , A (Carotenoids) & E.

3- ***Trace Elements*** : Selenium.

4- ***Phytochemicals*** (Antioxidants in Food) :
   a- Polyphenols in tea.
   b- Isoflavones & Phenolic acid in soybeans.
   c- Bioflavonoids in citrus fruits.

5- ***Melatonin*** :
   a- Hormone of pineal gland.
   b- Improve quality of sleep.
   c- Most potent antioxidant (Twice as Vit E & Five times as Glutathione)
   d- Fat & Water soluble so act intracellular and in the body fluids. It passes BBB & Placental B.
   e- Can be given orally.

Immuno-Modulators

1- Immuno-Stimulants :

* Preparations :

1- Non-Specific stimulants of immunity by **Vaccines e.g. BCG** : Activation of macrophages to make more effective killer cells.
2- **Levamisole** : An Anti-Helminthic . It stimulates T-cells mediated immunity.
3- **Inosiplex** : Increases natural killer cell cytotoxicity & T-cell function.
4- **Cytokines (Lymphokines)** e.g. ***Interferons, Colony Stimulating Factors (CSFs) & Interleukins***. Immunoregulatory proteins synthesized within lymphoreticular cells.
5- **Thymosin** : Protein derived from thymus. Induces maturation of Pro-T-Cells.
6- **Monoclonal Antibodies** : Selectively bind to tumor cells.

* U s e s :

1- Immuno-deficiency disorders. 2- Chronic infections. 3- Cancer.

2- Immuno-Suppressive Agents :

* Preparations :

1- **Cyclosporin A** *(Sandimmune)* :
a- Fungal cyclic polypeptide. Effective orally & IV specially in kidney transplant
b- ↓ IL-2 production & expression of its receptor by T-lymphocytes.
c- Side Effects : Nephrotoxicity mainly on PCT, Hepatotoxicity, Lymphomas & GIT upsets. Does NOT ↓ bone marrow.

2- **Tacrolimus** (FK 506) :
a- Macrolid antibiotic.
b- Mechanism : Similar to cyclosporin BUT more potent by 100 times.
c- Useful in liver transplant.

3- **Azathioprine** *(Imuran)* :
a- Anti-purine Anti-metabolite → ↓ DNA & RAN synthesis.
b- Its metabolism is inhibited by Allopurinol.

4- **Methotrexate** : Anti-Folate Anti-Metabolite.

5- **Cyclophosphamide** *(Endoxan)* : Alkylating agent.

6- **Glucocorticoids** : Prednisone & Prednisolone → Lympholytic effect.

7- **Anti-Lymphocyte Antibodies** : Anti-Lymphocyte Globulin (ALG), Anti-Thymocyte Globulin (ATG) & Monoclonal Anti-T-Cells Antibodies ((OKT3). Produced by immunization of large animals with human lymphoid cells.

8- **Rh_o (D) Immunoglobulins** : IgG. Injected to Rh -ve mother 72 hours after the labor or Rh +ve baby.

* Uses of immunosuppressives :

1- To prevent tissue rejection after organ e.g. Kidney transplantation : Cyclosporin.
2- Auto-immune diseases e.g. Rheumatoid : Azathioprine.
3- Rh hemolytic anemia in newborn.

* Hazards of Immunosuppressive Agents :

1- Infections : Treat by LD of bactericidal broad-spectrum antimicrobials.
2- Carcinogenesis.
3- Hazards related to the drugs used e.g. Corticosteroids & Cytotoxic agents.

Chelating Agents

Organic compounds that react with Heavy Metal Ions to form a non-toxic complexes easily excreted in urine.

1- Dimercaprol (British Anti-Lewisite = BAL) :

Used IM as Oily solution to chelate ***Mercury (Hg), Arsenic (As) & Antimony (Sb)*** :
1- Mercury (Hg) : As in Organic mercurial diuretics.]
2- Arsenic (As) : As in Organic Arsenical Amebecides.] Obsolete Drugs.
3- Antimony (Sb) : As in Trivalant Antimonial Anti-Bilharzials.]

2- Di-Sodium Edetate (EDTA = Ethylene Diamine Tetra Acetic Acid) :

Used IV to chelate ***Calcium (Ca^{+2})*** in cases of :
1- Hypercalcemia.
2- Digitalis poisoning.
3- Anti-Coagulant In-Vitro.

3- Calcium Disodium Edetate : Used by IV Infusion to chelate ***Lead (Pb).***

4- Dicobalat Edetate : Used IV to chelate **Cyanide.**

5- Desferrioxamine (Desferal) :

Used Orally & IV Infusion pump to chelate ***Iron in Ferric State (Fe^{+3}).***

6- D-Penicillamine : Used Orally to :

1- Chelate ***Copper (Cu)*** : Useful in Hepato-Lenticular Degeneration (Wilson's disease).
2- Treat Rheumatoid arthritis.

NB) Chelating Activity of Drugs :

1- Tetracyclines chelate Ca^{+2}, Mg^{+2}, Al^{+3} Iron.
2- Salicylates chelate Iron & Copper.
3- 8-Hydroxyquinolones e.g. Diodoquin chelate Iron & Copper.

Locally Acting Drugs

1- Demulcents:

Bland compounds of high M.W. + Water → Viscid mucilaginous solution.

A) Actions & Uses:

1- ***Protective Action***: on mucous membranes and abraded skin e.g. *gastric mucin* in gastritis and peptic ulcer.
2- ***Masking Bad Taste of Drugs***: by covering the taste buds of the tongue and adsorbing drug molecules.
3- ***Delaying Absorption of Drugs***: adding *gelatin* to heparin.
4- ***Delaying Excretion of Drugs***: adding *gum* to saline.
5- ***Emulsifying & Suspending Agents***: e.g. *Gum Acacia (Gum Arabic) & Gum Tragacanth*.

B) Individual Demulcents:

* Domestic: Egg white, milk & starch.

* Medical:

1- ***Gum Acacia (Gum Arabic) & Gum Tragacanth***: Emulsifying & Suspending agents.
2- ***Gastric Mucin***: from hog stomach *was* used in peptic ulcer.
3- ***Gelatin***:
   a- Preparation of pastilles, pessaries, suppositories & capsules.
   b- Added to heparin → Delay absorption → Depot form.
4- ***Glycyrrhiza (Liquorice)***:
   a- Tincture or infusion as a vehicle and flavoring agent e.g. Expectorant drugs.
   b- Powder as demulcent lozenges for gingivitis, stomatitis & pharyngitis → Antitussive.
   c- **Carbenoxolone**: Synthetic derivative of glycyrrhizic acid → Promote the healing of peptic ulcer.
4- ***Glycerin (Glycerol)***: Added to mucous membranes (*Demulcent*) & Skin (*Emollient*).
   a- Vehicle: Diluted with rose water as a lotion for roughened hands (Emollient).
   b- Glycerin-tannic acid & Glycerin-iodine for gingivitis.
   c- Sweetening agent.
   d- Orally → Absorbed → Food & source of energy.
   e- Glycerin suppository for constipation.

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2- Emollients:

Fats or oils applied to skin → Protective and softening agents.

1- ***Vegetable oils***: Olive oil, cotton seed oil, etc. Theobroma oil (Cocoa butter) is solid at room temperature that melts at body temp., and is used as a base for suppositories.
2- ***Animal Fat***: Lanoline (Wool fat) used as base for ointment.
Both vegetable oils & animal fats are absorbed from the skin together with the drugs.
3- ***Hydrocarbons from Petroleum***:
   a- **Liquid paraffin (Mineral oil)**: Orally as lubricant purgative.
   b- **Soft paraffin (Vaseline) & Hard paraffin** as base for ointment.
   They are *NOT* absorbed from the skin.
4- **Waxes** e.g. Beeswax as a base for ointment.

3- Astringents:

They precipitate surface (low penetration) proteins of mucous membranes & abraded skin.

A) Actions & Uses:

1- **Protection** of abraded surfaces against irritants.
2- **Local haemostatic** by precipitation of blood proteins at site of bleeding.
3- **Check exudation**.
4- **Local analgesic** by precipitation of nerve receptor proteins.
5- **Local disinfectant** by precipitation of bacterial proteins.

B) Classification of Astringents:

1) **Vegetable Astringents**: e.g. ***Tannic acid***.

- Tannic acid is present is some plants e.g. Tea, Krameria, Catechu & Hamamelis.
- It precipitate proteins in the form of protein tannates.
- ***Therapeutic uses of Tannic Acid***:

a- *WAS* used for burns *BUT*:
- Cracking of crust allowing bacterial infection beneath it.
- Hepatotoxicity (Central lobular necrosis) if it is absorbed.

b- Glycerin-tannic acid as antiseptic-astringent for the mouth, gums and throat.
c- Form insoluble complexes with:
- Heavy metals → Prevent the absorption of iron. It does *NOT* precipitate As, Sb & Hg.
- Alkaloids → Strong tea is used in strychnine poisoning. Do stomach wash afterwards as tannates formed is hydrolyzed by gastric acidity to liberate the poison again. It does *NOT* precipitate morphine, nicotine, cocaine, physostigmine & atropine.
- Glycosides.

d- Symptomatic treatment of diarrhea.
e- Treatment of hemorrhoids e.g. Hamamelis ointment or suppository.

2) **Salts of Heavy metals**:

Heavy metal salt (soluble) + Protein → Metal proteinate (insoluble) + Free acid (irritant)

a- Alum & Ferric chloride → Local haemostatic.
b- Lead acetate → Minimize spread of inflammatory edema.
c- Silver nitrate → Local disinfectant.

3) **Ethyl Alcohol 70%** → Dehydration of protein molecules→ Denaturation→ Precipitation. Used as antiseptic and astringent against bed sores.

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4) Mechanical Protectives:

1- ***Dusting powder***: Inert & insoluble substances that act as mechanical protective for the skin. They include talc (magnesium silicate), zinc oxide, starch & calcium carbonate.
   a- They protect the skin against irritation due to friction.
   b- They adsorb skin moisture, bacterial toxins & odors → Deodorant action.
2- ***Collodion***: Pyroxolon (nitrated cellulose) + Ether + Alcohol → Rapidly dries leaving firm protective film. May be medicated with salicylic acid for removal of corns and warts.
3- ***Plasters***: Sticky preparation (Rubber + Resin + Waxes + Powder e.g. zinc oxide).
   a- Simple: just for mechanical support.
   b- Medicated: counterirritant e.g. mustard plaster.

5) Irritants & Counterirritants:

A) Irritants: Substances that produce inflammation at site of application.

* *Classification:*

1- **Physical**: Heat in the form of hot water bottle, fomentation, poultice (kaolin), diathermy & short wave therapy.
2- **Chemical**:
   a- Volatile Irritants:
      - Volatile oils: Turpentine oil (liniment), camphor (liniment) & mustard (plaster).
      - Methyl salicylates (oil of wintergreen).
      - Tincture iodine in 5% alcohol.
      - Ammonia inhalation as reflex analeptic.
   b- Non-volatile Irritants: Cantharidine, obtained from Spanish fly.

* *Actions of Irritants:*

1- ***Local Actions***: Depends on the *nature* of the irritant, its *concentration* & *period* of contact.
   a- Rubefacient: Histamine release → Arteriolar VD (axon reflex) → Hyperemia of skin.
   b- Vesicant: Dilatation & ↑ permeability of skin capillaries → Transudate → Blister.
   c- Pustulant: Penetrate orifices of sebaceous glands → Small multiple abscesses.
   d- Caustic (Corrosive, Escharotic): Destruction of tissues.
2- ***Reflex or Remote Actions***:
   a- Segmental reflex.
   b- Central or Medullary reflex.

* *Uses of Irritants:*

1- Counterirritant to relief of pain of arthritis, myositis, abscess & visceral pains e.g. colics.
2- Caustics to remove excessive granulation tissue, warts & corns.
3- Reflex analeptic.

B) Counterirritants:

Relief of deep pain by the application of an irritant to an area of skin supplied by the same spinal segment as that of the diseased organ (joint, muscle or viscera).

* Mechanism of Action of Counterirritants:

1- ***Local Actions***:

a- Irritation of sensory nerve endings → Histamine release → VD → Sensation of heat, pain, redness & swelling.
b- Axon reflex → Antidromic reflex → Arterioles → VD.

2- ***Reflex Actions***:

a- Segmental Reflex: Sensory impulses along sensory nerves → Spinal cord → Efferent vasomotor fibers → VD of internal organs.
b- Central or Medullary Reflexes:
   i- ↑ RC & ↑ VMC → Redistribution of circulation to the benefit of diseased organ → Wash of accumulated toxins and metabolites.
   ii- Relief of pain :
      - Blocking the common pathway of pain (spinothalamic tract) by the sharp pain arising from the irritated area of skin.
      - Diverting the attention of the patient (psychic effect).

6) Keratolytics:

Agents used to soften keratin & loosen cornified epithelium → Treatment of corns, warts & fungal diseases of skin, e.g. Salicylic acid & Resorcinol.

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7) Antipruretics:

Agents used to allay itching

1- **Corticosteroids**: Locally or systemically specially in allergic cases.
2- **Antihistaminics**: Locally or systemically.
3- **Chlorpromazine** systemically.
4- **Local anesthetics** e.g. 3% Benzocaine ointment.
5- **Phenol** 0.5-1 % solution locally.
6- **Tar ointment** specially in eczema.
7- **Volatile oils** e.g. camphor and menthol locally.

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8) Depilatory Agents:

Agents used to remove hair.

1- **Drugs applied locally (Chemical shaving)**: *Barium & calcium sulfides* cream on skin for < 5 minutes → Dissolve hair shafts → Scrapping off. Hair follicles remain intact. They release hydrogen sulfide of bad odor.
2- **X-Ray** to remove scalp hair in treatment of ring-worm. Hair falls in the exposed area after about 3-4 weeks, and grows again after another 3-6 weeks.
3- **Thallium acetate** orally to remove scalp hair in treatment of ring-worm in children (Obsolete).

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9) Antiseborrhoeics:

Agents that ↓ sebaceous gland activity → Treat seborrhoeic dermatitis & hair dandruff.

1- **Sulphur ointment**.
2- **Ammoniated mercury ointment or mercuric chloride ointment**.
3- **Selenium or cadmium sulphides** shampoo on the scalp for 2-3 minutes then rinsed.
   - Irritant to eye.
   - Selenium sulfide if absorbed (orally or through damaged epithelium) → Hepatotoxic & nephrotoxic.

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10) Melanizing & Demelanizing Agents:

A) Melanizing Agents:

Drugs that stimulate the production of melanin from tyrosine → Treatment of idiopathic vitiligo & enhance skin pigmentation.

1- ***Methoxsalen***: Obtained fro Egyptian plant (Ammi majus) → Sensitize skin to UV light.
   a- Orally 20 mg once daily followed after 2 hours by exposure to sunlight or UV for < 5 minutes.
   b- Locally 1% lotion weekly followed by exposure to sunlight or UV for <1 minute.
2- ***Trioxsalen***: Related to Methoxsalen.

B) Demelanizing Agents:

Drugs which inhibits melanin formation. They inhibit tyrosine hydroxylase enzyme → ↓ Conversion of tyrosine to DOPA the precursor of melanin. They are useful for the treatment of hyperpigmentation e.g. chloasma of pregnancy & severe freckling.

1- ***Monobenzone*** (Benoquin).
2- ***Hydroquinone***.

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11) Enzymes That Act Locally:

1- **Hyaluronidase**: Hydrolyzes hyaluronic acid (intercellular ground substance) → Help diffusion & absorption of SC drugs e.g. local anesthetics & fluids (hypodermoclysis).
2- **Streptokinase & Streptodornase** mixture (Varidase) obtained fro hemolytic streptococci → Liquefy clotted blood & pus → Useful in hematomas, hemothorax & empyema.
3- **Trypsin & Chymotrypsin**: Proteolytic enzymes, similar to the above.
4- **Thrombin** powder used as local hemostatic.
5- **Digestive enzymes** e.g. pepsin & pancreatin used as digestants.

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12) Local Antifungal Agents:

1- **Nystatin** *(Mycostatin)*: Used locally to treat Candida albicans (monilia) infections e.g. paronychia, vaginitis, stomatitis (thrush) & intestinal moniliasis.

2- **Fatty acids & Their Salts**:
   a- Undecylenic acid: It is used as fungistatic for fungal skin diseases as powder and ointment 10% or as compound undecylenic acid ointment (5% Undecylenic acid + 20% Zinc undecylenate).
   b- Sodium propionate 5-15%: Fungistatic, used locally for fungal skin diseases.

3- **Imidazole Derivatives**:
   Broad spectrum fungistatic drugs active against candida and dermatophytes.
   a- Clotrimazole *(Canesten)* used topically for skin and vaginal infections.
   b- Miconazole *(Daktarin)* similar to clotrimazole.

4- **Tolnaftate** *(Tinactin)*: Topical fungiststic.

5- **Salicylanilide** ointment for Tinea capitis.

6- **Thymol**.

7- **Benzoic 6% + Salicylic acids 3%** *(Witfield's ointment)* for Tinea pedis.

8- **Rosaniline Dyes**:
   a- Gentian violet 1% lotion for candida infections.
   b- Basic fuchsin (Castellani's paint).

9- **Sulphur precipitate**: Fungicidal and scabicidal.

10- **Tincture Iodine** 2% solution in alcohol or glycerin → Local germidide & fungicide to disinfect skin and mucous membranes.

13) Antiseptics & Disinfectants

- Antiseptic → Kill or ↓ growth of microorganisms, applied to living tissues.
- Disinfectant → Destroy microorganisms, applied to inert matter

1- Phenol & Phenol Analogues:

A) Phenol (Carbolic Acid):

Phenol → Denature proteins → Bacterial (Antiseptic) & Nerves (Local anesthetic).

1- Domestic disinfectant.
2- Liquified phenol (Phenol in 10% distilled water):
   a- Cauterize dog bite, snakebite & appendicular stump after appedicectomy.
   b- Analgesic & obtundant in toothache.
3- Antipruretic (0.5-1%).

B) Phenol Analogues:

1- **Cresol**: Methylphenol obtained from coal tar. Saponified cresol solution (***Lysol***) is used as disinfectant and hand wash (2% in water).
2- **Chlorocresol**: Preservative for aqueous injections and eye drops.
3- **Chloroxylenol** (*Dettol*): Antiseptic 5% solution.
4- **Resorcinol**: Ointment & lotion (2-20%) for skin diseases e.g. ringworm.
5- **Thymol**: Bactericidal, fungicidal & anthelmintic.
6- **Hexachlorophane**: Antiseptic & deodorant (↓ bacterial decomposition of organic material). It is largely replaced by **Trichlorocarbanilide**:
   a- Uses:
      - Medicated soaps & Tooth pastes.
      - Ointment & Cream (2-3%) for pyrogenic skin infection.
   b- Toxicity if absorbed from skin or vagina → Confusion, convulsions, ↓ RC & Diplopia.

2) Alcohols:

Ethyl alcohol 70% → Dehydration of proteins → Denaturation → Precipitation → Antiseptic and astringent useful in bed sores.

3) Acids:

1- **Salicylic acid**: Antiseptic, fungicidal & keratolytic.
2- **Benzoic acid**:
   a- Antifungal: Benzoic acid 6% + Salicylic acid 3% → Whitfield's ointment.
   b- Food preservative.
3- **Boric acid**:
   a- Eye lotion 4%.
   b- Dusting powder 10% or Ointment 10% for skin infection.
   c- Sodium borate (Borax) in glycerin (12% w/v) → Paint for gum.
4- **Mandelic acid & Nalidixic acid**: Urinary antiseptics.
5- **Fatty acids**: *Undecylenic acid & sodium propionate* → Antifungal.

4) Aldahydes:

1- **Formaldehyde** 37% solution → **Formalin**:
   a- Formalin 2-5% solution → Disinfectant for instruments & gloves.
   b- Formalin 10% solution → Preserve and harden tissues for histolopathology.
2- **Methenamine**: Urinary antiseptic. It releases formaldehyde in acid urine. Add acidifying agent e.g. Mandelic acid.

5) Oxidizing Agents:

They release nascent oxygen → Antibacterial action.

A) Peroxides:
1- **Hydrogen peroxide**: Antiseptic, deodorant & hair bleeching. By tissues peroxidase enzyme → Release of nascent O_2 → Antiseptic & frothing → Detach pus and debris.
2- **Zinc peroxide**: Slow release of nascent O_2→ Disinfectant& deodorant → Mouth wash for oral infections & promote healing of infected wounds.

B) Permanganate:
1- **Potassium permanganate**:
   a- Wet dressing (1/10 000 solution) for dermatitis and eczema.
   b- Gastric lavage (1/2000 solution) for alkaloidal poisoning e.g. morphine.
2- **Zinc permanganate**: Disinfectant & astringent.

C) Perborate: e.g. **Sodium perborate**
1- 2% solution → Antiseptic for wounds & mouth wash for gingivitis & Vincent's angina.
2- 5% dusting powder.

6) Halogens & Halogen Containing Compounds:

A) Iodine:

1- **Tincture iodine**:
   a- 2.5% = Liquor iodi mitis → Skin disinfectant preoperative, wounds & fungal diseases.
   b- 10% = Liquor iodi fortis → Counterirritant.
   c- 1/250 solution ORALLY → Alkaloidal poisoning.
2- **Iodine glycerin** 2% → Mouth paint for gingivitis.
3- **Iodoform** → Slow release of elemental iodine → Weak antiseptic fo wound dressing.
4- **Iodophors**: Iodine + Stabilizing agent or carrier → Slow release of iodine → Antiseptic. Example *Povidone-iodine* 10% solution (Betadin).
5- **Lugol's iodine** (5% iodine in 10% potassium iodide in water) → Orally in goiter.

B) Chlorine:

Chlorine in aqueous solution → Hypochlorous acid → Oxidation of SH-containing enzymes and destroys cell membrane of bacteria. The presence of organic matter reduces its action.

1- **Hypochlorites**: Freshly prepared → Germicidal & dissolve necrotic tissue.
   a- Sodium hypochlorite (Dakin's solution).
   b- Calcium hypochlorite (Eusol).
2- **Chloramines**: Organic compounds containing chlorine linked to nitrogen → Release Cl.
   a- Chloramine T 1-2% solution → Wound dressing.
   b- Halazone tablets → Disinfect drinking water.

7) Heavy Metal Salts:

They inhibit SH-containing enzymes & precipitate proteins of bacteria.

A) Mercury Compounds:

1- **Mercuric chloride** (Corrosive sublimate): Hand wash for surgeons & disinfect surgical instruments that are not to be boiled.
2- **Mercurous chloride** (Calomel): Ointment & dusting powder.
3- **Mercuric oxycyanide**: Solution for irrigation of conjunctiva.
4- **Yellow mercuric oxide**: Ophthalmic ointment.
5- **Ammoniated mercury ointment**:
   a- Skin disinfectant in impetigo.
   b- Applied to the anal region in pinworm infection.
6- **Merbromin** (Mercurochrome): Bacteriostatic skin disinfectant.

B) Zinc Compounds:

1- **Zinc sulfate** eye drops → Antiseptic & astringent.
2- **Zinc oxide**: Skin ointment.
3- **Zinc permanganate**.
4- **Zinc peroxide**.

C) Silver compounds:

1- **Sivler nitrate** eye drops → Argyrosis = Blackening of the sclera (OBSOLETE).
2- **Colloidal silver proteinate** e.g. Argyrol eye drops (OBSOLETE).
3- **Silver sulphadiazine** for skin burns → Painless & antipseudomonal activity.

D) Copper Compounds: e.g. **Copper sulphate**:

1- WAS used as eye drops.
2- Orally in organophosphorus poisoning → Insoluble copper phosphate.
3- Molluscicide for bilharzial snails.

8) Dyes:

1- **Azo dyes** e.g. Pyridium WAS used as urinary antiseptic.
2- **Acridine dyes** e.g. Acriflavine → Disinfectant.
3- **Fluorescein dyes**:
   a- Fluorescein: NOT antiseptic. Eye drops for diagnosis of corneal ulcer.
   b- Merbromin (Mercurochrome).
4- **Phenolphthalein dyes**: NOT antiseptic
   a- Sulphobromophthalein sodium (Bromsulphthalein): Assess liver function.
   b- Phenolphthalein: Moderate irritant purgative.
5- **Rosaniline dyes** e.g. *Gentian violet* (crystal violet) antiseptic paint for infected wounds & thrush (monilial stomatitis).
6- **Methylene blue** for met-hemoglobinemia.

9) Surface-Active Agents (Surfactant , Detergents):

They accumulate at bacterial cell membrane → ↓ surface tension → Escape of enzymes, coenzymes & metabolites → Bactericidal. They are either anionic or cationic. They are NOT mixed together → Incompatibility.

1- **Anionic surfactants**: e.g. Soft soap & Sodium lauryl sulphate. In aqueous solution → Large complex anion. They act on Gram +ve organisms (Except Staph aureus) and NOT Gram –ve ones.
2- **Cationic surfactants** e.g. Benzalkonium chloride (*Zephiran)* & Cetyl-trimethyl-ammonium bromide (*Cetavlon, Cetrimide*). In aqueous solution → Large complex cationic → More active & broader spectrum (Gram +ve & -ve BUT NOT viruses).
3- **Non-ionic surfactants**: e.g. Polysorbates → Emulsifying agent & NOT antiseptic.

10) Miscellaneous Gemicides:

1- **Sulpher** → Release H_2S or pentathionic acid → Germicide, fungicide, keratolytic & ectooparasiticide.
2- **Ichthammol**: Ointment for skin diseases.
3- **Volatile Oils**: Weak antiseptics.

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14) Ectoparasiticides:

1- **Dicophane** (DDT) 10% powder in talc for *pediculosis*.
2- **Gamma Benzene Hexachloride** (Gammexane) powder, lotion & ointment for *pediculosis and scabies*.
3- **Benzyl Benzoate** lotion for *pediculosis and scabies*.
4- **Sulpher ointment** (5-10%) for *scabies*.

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